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A randomised controlled feasibility trial to investigate the effects of a functional standing frame programme versus usual physiotherapy to improve function and quality of life and reduce neuromuscular impairment in people with severe sub-acute stroke

by

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A thesis submitted to the University of Plymouth in partial fulfilment for the degree of

DOCTOR OF PHILOSOPHY

School of Health Professions

November 2019

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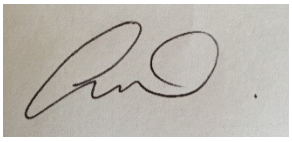
Work submitted for this research degree at the University of Plymouth has not formed part of any other degree either at the University of Plymouth or at another establishment.

This trial was financed with the aid of a Clinical Doctoral Research Fellowship from the National Institute for Health Research (ICA-CDRF-2015-01-044) and supported by the School of Health Professions, Plymouth University.

A programme of advanced study was undertaken, which included methodological and speciality specific training.

Word count of main body of thesis: 79,016

Signed: 

Date: 27/11/2019

Acknowledgements

Completing this thesis has been a challenging and rewarding journey, one that would have been impossible without the collaboration and support of many people.

I am indebted to my Director of Studies Professor Jonathan Marsden who has tirelessly shared his wisdom and support. Some discussions were utterly mind-blowing, but your enthusiasm and encouragement enabled me to complete this thesis. Deep thanks to Professor Jennifer Freeman whose attention to detail, honesty and encouragement has been hugely valuable. Sincere thanks to Dr Jillian Pooler for your feedback and encouragement. Thank you all very much for believing in me.

Sincere thanks and gratitude to all the participants, physiotherapists and other clinical, administrative and research staff involved in the trial. Without your involvement, SPIRES would not have been possible.

I gratefully acknowledge the National Institute for Health Research for funding my Clinical Doctoral Research Fellowship. The fellowship has been an incredibly valuable opportunity, both professionally and personally.

Thank you to the Trial Management Group: Professor Jonathan Marsden, Professor Jennifer Freeman, Dr Jillian Pooler, Professor Bridie Kent, Mrs Siobhan Creanor, Dr Doyo Enki, Miss Jane Vickery and Mr Andrew Barton. Special thanks to Mr Brian Wainman, Data Manager whose calming nature and humour kept me sane.

I sincerely appreciate the Trial Steering Committee: Dr Joanne Paton, Dr Denise Howell, Dr Rhoda Allison, Mrs Siobhan Creanor, Dr Doyo Enki and Miss

Jane Vickery. Special thanks to the Chair, Professor Pip Logan at Nottingham University. Your support and encouragement is much appreciated. Special thanks to our patient and public representatives, Mr Paul White, Mrs Lynda Coates-Flecknor and Mr David Flecknor. I am truly indebted to you for the support and enthusiasm for my research and me personally. Your perspectives and personal experiences of stroke have been extremely valuable.

I am very grateful to Professor Anne Forster, University of Leeds for her mentorship throughout my fellowship.

Thank you to Denise Williams and Karen Roach in Cornwall Partnership Foundation NHS Trust for supporting my desire to pursue a clinical academic career. I was the first person within my Trust and in Cornwall to apply for this fellowship, and it was unknown territory for us all, but you did not hesitate in supporting me.

Thank you to Dr Katharine Stone, who has provided clinical supervision during my fellowship and encouraged me throughout the last year during my clinical role in the Stroke and Neurology Therapy Team in Cornwall Partnership Foundation NHS Trust.

Thank you to the Research and Development Team at Royal Cornwall Hospitals Trust for acting as Trial Sponsor, Research Design Service South West and Peninsula Clinical Trials Unit.

I would like to express my heartfelt thanks to my family and friends who have been there when I needed them and have given their time (and mostly their ears and hugs). You have kept me going through the tough times and provided much needed reassurance and support. My family’s unconditional love and work ethic has got me where I am today. Thank you to you all.

A randomised controlled feasibility trial to investigate the effects of a functional standing frame programme versus usual physiotherapy to improve function and quality of life and reduce neuromuscular impairment in people with severe sub-acute stroke

Angela Berrill Logan

Abstract

Background

Task-related training can aid functional recovery post-stroke but has not been investigated in people with severe stroke. Orthostatic hypotension (OH) may limit rehabilitation, therefore, the effects of undertaking prolonged standing and sit to stand repetitions (functional standing frame programme) early after severe stroke during inpatient sub-acute rehabilitation is unknown.

Methods

A systematic review of non-pharmacological interventions to treat OH in people with neurological conditions was undertaken to inform a protocol for the management of OH during the functional standing frame programme. The feasibility of a blinded randomised controlled trial (RCT) investigating the effects of a functional standing frame programme compared to usual physiotherapy for people with severe stroke was conducted.

Primary (Barthel Index, Edmans ADL Index for Stroke) and secondary outcomes (including lower limb joint range of movement, knee extensor strength, and quality of life) were assessed at baseline, post-intervention and 15-, 29- and 55-weeks post-randomisation.

Semi-structured interviews were conducted with a subset of participants, relatives and physiotherapists to explore experiences of the intervention and trial procedures.

Data were analysed using thematic analysis and descriptive analysis.

Results

The systematic review included randomised controlled trials (n=13), quasi-experimental (n=27), case control (n=1) and case report (n=2). A meta-analysis of seven studies concluded electrical stimulation, lower limb compression and resistance exercise training were favourable in treating or reducing OH.

Forty-five participants (51-96 years; 42% male, mRS 4=80% 5=20%) were recruited; n=22 randomised to intervention, n=23 to control. Twenty-seven participants completed the trial: n=12 died (n=7 intervention), n=2 moved out of area, n=4 withdrawn.

Adherence to the intervention was low: 38-51% of possible sessions being completed; average session duration 39.40 minutes (±18.8); standing duration 12.52 minutes (±8.8); and mean sit-to-stand repetitions 4.64 (±3.9 SD) per session. 91% of sessions were enjoyed. Adherence was affected by patient, physiotherapist and organisational factors.

Conclusion

A definitive RCT of a functional standing frame programme is feasible for people with severe stroke. However, intervention adherence need to be addressed before progressing to a definitive trial, which will investigate clinical and cost effectiveness.

Publications and presentations

Publications related to the work within this thesis are listed below:

Logan, A., Marsden, J., Freeman, J., Kent, B. (2017) Effectiveness of non-pharmacological interventions in treating orthostatic hypotension in the elderly and people with a neurological condition: a systematic review protocol. *JBI Database Systematic Reviews and Implementation Reports*, Apr 15(4), 948-60.

Logan, A., Freeman, J., Kent, B., Pooler, J., Creanor, S., Vickery, J., Enki, D., Barton, A. & Marsden, J. (2018) Standing Practice In Rehabilitation Early after Stroke (SPIRES): a functional standing frame programme (prolonged standing and repeated sit to stand) to improve function and quality of life and reduce neuromuscular impairment in people with severe sub-acute stroke-a protocol for a feasibility randomised controlled trial. *Pilot and Feasibility Studies*, 4:66.

Logan, A., Freeman, J., Kent, B., Gunn, H., Billings, S., Cork, E. & Marsden, J. (2019) Is practising standing-up and moving between sitting and standing early after a severe stroke feasible? A feasibility randomised controlled trial. *Physiotherapy*, 105, e66, January 2019.

Logan, A., Freeman, J., Kent, B., Gunn, H., Billings, S., Cork, E. & Marsden, J. (2019) Effectiveness of non-pharmacological interventions in treating orthostatic hypotension in the elderly and people with a neurological condition: a systematic review protocol. *JBI Database Systematic Reviews and Implementation Reports* (In submission)

Conference poster presentations related to the work within this thesis are listed below:

Logan, A., Freeman, J., Kent, B., Pooler, J., Creanor, S., Vickery, J., Enki, D., Barton, A. & Marsden, J. Is practising standing-up and moving between sitting and standing early after a severe stroke feasible? A feasibility randomised controlled trial (SPIRES).

Presented at the following conferences:

- Joining Force South West Annual Stroke Conference, June 2017, Exeter
- UK Stroke Forum, Liverpool, November 2017
- Physiotherapy UK, October 2018, Birmingham
- UK Stroke Forum, December 2018, Telford
- Association of Chartered Physiotherapists Interested in Neurology International Conference, March 2018, Manchester
- Allied Health Professions Day, October 2018, Truro.
- Physiotherapy UK, November 2019, Birmingham

Logan, A., Freeman, J., Kent, B., Pooler, J., Creanor, S., Vickery, J., Enki, D., Barton, A. & Marsden, J. The effectiveness of non-pharmacological interventions to treat orthostatic hypotension in people with stroke: a systematic review.

Presented at the following conferences:

- South West Clinical School Symposium, May 2019, Truro.
- Physiotherapy UK, November 2019, Birmingham

Conference oral presentations related to the work within this thesis are listed below:

Logan, A., Freeman, J., Kent, B., Pooler, J., Creanor, S., Vickery, J., Enki, D., Barton, A. & Marsden, J. Is practising standing-up and moving between sitting and standing early after a severe stroke feasible? A feasibility randomised controlled trial (SPIRES).

Presented at the following conferences:

- Plymouth University Research Festival, January 2018, Plymouth
- Plymouth University Postgraduate Annual Research Conference, March 2018, Plymouth
- Joining Force South West Annual Stroke Conference, June 2018, Exeter
- South West Clinical School Symposium, May 2019, Truro.
- Society of Rehabilitation Research and British Society of British Rehabilitation Medicine joint meeting, October 2019, University of Warwickshire
- Physiotherapy UK, November 2019, Birmingham

Logan, A., Freeman, J., Kent, B., Pooler, J., Creanor, S., Vickery, J., Enki, D., Barton, A. & Marsden, J. The effectiveness of non-pharmacological interventions to treat orthostatic hypotension in people with stroke: a systematic review.

Platform presentation delivered at:

- Physiotherapy UK, November 2019, Birmingham

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List of abbreviations

ADL	Activities of Daily Living
AE	Adverse Event
AMED	Allied and Complimentary Medicine Database
ASU	Acute Stroke Unit
AVERT	A Very Early Rehabilitation Trial
BI	Barthel Index
CDRF	Clinical Doctoral Research Fellowship
CI	Chief Investigator
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRN	Clinical Research Network
CT	Computer Tomography
CVA	Cerebral vascular accident
ESD	Early Supported Discharge
EQ-5D-5L	EuroQoL
FAST	Frenchay Aphasia Screening Test
HRA	Health Research Authority
HRQoL	Health Related Quality of Life
ICA	Integrated Clinical Academic
ICC	Intraclass correlations coefficient
ICD-10	International Classification of Diseases and Related Health Problems
IRAS	Integrated Research Application System

ISRCTN	International Standard Randomised Controlled Trial Number
JBI	Joanna Briggs Institute
JBI-MAStARI	Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument
MEDLINE	Bibliographic database
MeSH	Medical subject heading
MRC	Medical Research Council
mRS	Modified Rankin Scale
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellences
NIHSS	National Institutes of Health Stroke Scale
NRES	National Research Ethics Scheme
OH	Orthostatic Hypotension
OT	Occupational Therapist
PEDro	Physiotherapy Evidence Database
PD	Parkinson's Disease
PenCTU	Peninsula Clinical Trials Unit
PHQ-9	Patient Hospital Questionnaire 9 item
PI	Principal Investigator
PPI	Patient and Public Involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International database of prospectively registered systematic reviews
REC	Research Ethics Committee
RCP	Royal College of Physicians
RCT	Randomised Controlled Trial

SADQ-10	Stroke Aphasia Depression Questionnaire
SAE	Serious Adverse Event
SAQoL-39	Stroke and Aphasia Quality of Life Scale 39 item
SCI	Spinal Cord Injury
SR	Systematic review
SRU	Stroke Rehabilitation Unit
SPIRES	Standing Practice In Rehabilitation Early after Stroke
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TiDIER	Template for intervention description and replication
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
VAS	Visual Analogue Scale

Chapter 1 Introduction and background

1.1 Introduction

Stroke is a sudden and devastating condition affecting over 100,000 people in the United Kingdom (UK)[1] and approximately 14 million people globally[2] per annum. It is the largest cause of complex adult disability, with wide variations in aetiology, age at onset and comorbidities and presents a major global public health challenge. Stroke is categorised as: ischaemic (lack of blood and oxygen to an area of the brain) or haemorrhagic (bleeding from a burst or leaking blood vessel with accumulation of blood either inside the brain or spinal cord, or on the surface of the brain (subarachnoid haemorrhage)). Approximately 85% of strokes are ischaemic,10% due to primary haemorrhage, and 5% due to subarachnoid haemorrhage[3].

Research in the field of early mobilisation post-stroke has had an unequivocal impact on stroke care and rehabilitation[3]. Reasons why this area of clinical practice is important for people with stroke is discussed in this chapter. Several areas are explored in the existing body of evidence to provide background and context for this thesis and rationale for my research question. Evidence is used to critically evaluate what was already known and available in clinical practice, prior to commencement of this thesis, and identify knowledge gaps to define a relevant and meaningful research question.

Firstly, this chapter presents an overview of the impact of stroke, current management and mechanisms underlying recovery. Secondly, the knowledge base and impact of early mobilisation is presented. Thirdly, the evidence for standing practice and task-specific strength training is appraised in relation to

the early sub-acute phase of inpatient stroke rehabilitation. Lastly, my research approach is introduced providing the rationale and structure of this thesis.

1.2 Stroke impact and management

A stroke can have devastating and life changing effects, the severity of which are dependent on the location and extent of the brain damage[4]. The World Health Organization[5] provide a framework for the long-term management of stroke. The framework is articulated in terms of: Pathology (the disease processes within organs); Impairment (symptoms/signs; the manifestations of disease in the individual); Activities (the impact of impairments on the person's usual activities); Participation (the impact of activity limitations on a person's place in family and society). Stroke can result in impairments in motor (e.g. weakness, altered tone), sensation (e.g. touch, joint position sense, pain), cognition (e.g. perception, attention, memory), communication (e.g. speech and language), mood and wellbeing (e.g. anxiety, depression), continence, swallowing vision, fatigue (extreme tiredness). All of these impairments can cause significant disability that severely affect activities, participation and quality of life[3]. Impairments are present from stroke onset with some recovering rapidly and completely. Other impairments, however, will persist over weeks, months and years and may even increase over time due to the challenges and restrictions of life after stroke and ageing. The restrictions in activities and participation lead to a high economic burden on relatives/informal carers, the National Health Service (NHS) and social care, with direct and indirect care costs estimated at £1.7 billion per annum[6].

The cornerstone of stroke rehabilitation is to provide people the opportunity to acquire knowledge and skills to optimise their physical, psychological and social

function, aiming to reduce restrictions in activities and participation[7]. Current government and clinical guidelines recommend that following diagnosis of a stroke, people are admitted to an Acute Stroke Unit (ASU) to receive stroke specialist multi-disciplinary care. This is based on unequivocal evidence of reduced mortality and improved functional outcomes when patients are treated in specialist stroke units by co-ordinated multi-disciplinary teams[8,9]. The UK Stroke Pathway[10] and National Clinical Guidelines[3] advocate that people with mild or moderate stroke (i.e. modified Rankin Scale (mRS) 1-3; able to perform all usual activities, slight or moderate disability but able to walk without assistance) are discharged from the ASU to the Early Supported Discharge (ESD) service, which provides specialist stroke rehabilitation in a home-based setting. People with severe strokes (mRS 4-5; moderately severe disability or severe disability and bedridden) are typically transferred from the ASU to a specialist Stroke Rehabilitation Unit (SRU) for early sub-acute rehabilitation usually within seven days. The early sub-acute phase spans from seven days to three months[11], with the local average time from stroke onset to admission on a SRU being six days (one to 37 days)[12]. Some ESD services in the UK admit people with a mRS of 4 but this is currently not standard care nationally. The implementation of ESD has caused a change in patient caseload nationally for SRUs[3] resulting in the majority of people admitted to SRUs having severe impairments and complex needs. This change in caseload necessitates the design and evaluation of interventions for people in SRUs that target people with severe deficits.

The most common physical deficit caused by stroke is motor impairment, regarded as a loss or limitation of function in muscle control or movement[13]. Motor impairment after stroke typically affects the control of movement of one

side of the body (face, arm, trunk and leg) and is seen in approximately 80% of people[14]. It is the single most disabling factor in terms of limiting a person's mobility, their ability to participate in activities of daily living (ADL) and live independently[15]. Mobility encompasses a wide range of activities necessary for daily functioning: moving in bed; getting in/out of bed, on/off toilet; sitting out of bed, standing and walking[3]. These activities are particularly affected in the 15.5% of people with severe stroke[1] who require the assistance of two people to undertake ADL and are unable to sit unsupported, stand or walk without assistance and/or equipment[16]. They typically spend much of their time in bed and are dependent on careful positioning and specialist seating when sitting out of bed to provide postural support[17].

Although immobility post-stroke is primarily caused by neurological damage, it can be exacerbated by bed rest and sedentary behaviour. This can have a detrimental impact on the nervous, musculoskeletal and cardiorespiratory systems. Changes in the musculoskeletal system include muscle wasting[18], reduced muscle length, increased muscle stiffness[19] and joint contracture[20] which may cause aches and pains and muscle fatigue[21]. Additionally, loss of bone density (disuse osteoporosis) can occur and may be accelerated when the duration of immobility is prolonged[22]. Changes in the cardiorespiratory system such as orthostatic hypotension (OH) and reduced cardiorespiratory fitness may further impede recovery and participation in ADL and rehabilitation programmes. Orthostatic hypotension is a sudden drop in blood pressure when moving from lying to standing, leading to symptoms of feeling faint, generalised weakness, cognitive slowing and gradual or sudden loss of consciousness[23]. This can limit standing time and is discussed further in Section 1.7. Cardiorespiratory fitness is the ability of heart, lungs, blood vessels and skeletal

muscles to work together to deliver oxygen and remove metabolic by-products during physical activity[24]. Cardiorespiratory fitness facilitates the ability to perform physical activity for an extended period of time (endurance) and can be reduced as a result of inactivity or immobility post-stroke[25].

Immobility has a significant impact on recovery following stroke, thus providing people with stroke opportunities to improve mobility by practising functional tasks such as standing and moving between sitting and standing early after stroke is a key focus of rehabilitation[26]. Early rehabilitation has been defined as occurring within 48 hours of a stroke[3]. Rehabilitation comprises an interaction between the impact of the disease, the characteristics of the individual and the nature of their environment[27]. It covers a broad philosophy and range of interventions aiming to help an individual minimise the impact of a disabling health condition on their level of dependence[28]. In stroke, early rehabilitation typically addresses key impairments and offers the opportunity to reduce the burden of disability. This includes interventions that aim to optimise independence in self-care activities, swallow, speech and language, vision, cognition, motor function, balance and mobility[28].

The concept of an enriched environment in stroke rehabilitation is gaining increasing attention. This concept stemmed from animal model studies, whereby a stimulating environment was created to facilitate physical, sensory, cognitive and social activities[29,30]. In animal models an enriched environment has resulted in enhanced adaptive neuroplasticity[31] (Section 1.3). However, what constitutes this within the clinical scenario is still ambiguous as standardised guidelines are lacking.

1.3 Stroke and mechanisms of recovery

Motor impairment following stroke is defined by the International Classification of Functioning, Disability and Health as any loss, abnormality or failure of physiological or anatomical structure or function deriving from underlying pathology[32]. It can have a detrimental impact on motor function affecting a person's mobility, resulting in limited participation in activities of daily life such as eating, drinking, washing, dressing, cooking, standing, walking, and family and leisure activities.

Recovery of motor function following stroke is complex, non-linear and improvements may be attributed to different mechanisms that are not mutually exclusive: restoration (also known as resolution) or compensation[33,34] which may be spontaneous and/or learning-dependent[35]. Restoration refers to the resolution of pathophysiological changes and reactivation of brain areas that were dysfunctional after they were initially damaged. This is characterised by a person's ability to perform movements using the same muscle activation patterns and body parts or segments in the same manner prior to the stroke[35]. Compensation occurs when residual neural tissue takes over a motor function lost due to the ischaemia and is defined as using alternative strategies (including mechanical aids or physical assistance) or movements (different body parts/segments) to accomplish a motor task[34].

Following stroke, changes occur in the areas surrounding the stroke (focal changes) as well as areas distant to the stroke[36]. These changes occur over a short- (hours to days post stroke) and/or long-term (weeks to months post stroke) period. In acute ischaemic stroke, neurons are deprived of oxygen and glucose causing a complex cascade of events resulting in neuronal cell death.

Immediately following ischaemic stroke, blood flow and oxygen transport is also reduced to neurons surrounding the ischaemia (the penumbra), and oedema occurs due a cascade of pathophysiological events, leading to cell damage and risk of further neuron death[37]. Neuron death occurs primarily through excitotoxicity; cell death induced by high levels of glutamate[38].

The area surrounding the ischaemic injury undergoes changes in neuronal excitability due to excitatory (glutamate) and inhibitory (GABA) neurotransmitters, which alter the brains' representation of motor and sensory functions[39]. Neuronal changes and dysfunction also occurs in regions anatomically connected to the stroke site stroke[40]. This is known as diaschisis which refers to reduced activity, typically measured by blood flow and/or metabolism, in uninjured brain areas that have strong connections with injured brain areas[41]. This can occur in the same hemisphere as the stroke (ipsilesional) and the opposite hemisphere (contralesional).

Although brain damage resulting from the stroke is permanent and irreversible in the core of the lesion, peri-lesional tissue remains structurally intact, and during restoration in the acute and sub-acute phase, the penumbra undergoes reperfusion due to redundant collateral circulation, and oedema and diaschisis are resolved or reversed resulting in neurons being saved from death[42,43]. This often results in improvements in movement and function and is referred to as spontaneous biological recovery. Spontaneous biological recovery is thought to be augmented by a rebalance in the inhibitory-excitatory balance of GABA and glutamate[44] which have a profound impact on neuroplasticity. Neuroplasticity is a neurophysiological feature that occurs dynamically throughout life and is defined as the ability of the central nervous system (CNS) to adapt in response to lesions or environment[45]. This may include structural and functional changes

in neuronal properties, such as recruitment of new or different neural networks, changes in the strength of internal connections of neural networks or reorganisation of specific motor and sensory brain areas responsible for performing a particular task[46-48]. One way changes occur in the CNS is through potentiation, or the strengthening of the nerve synapses. Long-term potentiation (LTP) is the persistent strengthening of synapses based on recent patterns of activity. Both glutamate and GABA receptors control different steps in the LTP process[46]. The process of neural plasticity is important to acknowledge because it is felt to underpin improvements in function resulting from learning and relearning after stroke.

Frequent opportunities to relearn through practising and experiencing movement such as sitting to standing and standing early after stroke may result in greater functional gains due to elevated brain-derived neurotrophic factor (BDNF)[49]. Conversely, lack of movement leads to weakening and loss of synapses that may result in reduced functional gains or increased disability [50]. Thus, it is important to provide people with stroke the opportunity to move and practice meaningful tasks, and evidence suggests this should be encouraged during the critical period post-stroke.

The critical period for neuroplasticity is widely acknowledged in the literature and evidence from human and animal stroke studies suggests that neuroplasticity takes place maximally in a specific time window after an ischaemic lesion[34,51]. This appears to vary from six to 10 weeks[52] with longer periods for people with severe strokes[53]. Whilst there is no definitive time period, there is agreement that this critical period appears to be limited[54]. Understanding the pathophysiological changes and mechanisms underlying

stroke recovery are thus important for clinicians to understand to optimise functional recovery following stroke.

Recovery or compensation

It is also important to consider whether any behavioural improvements, e.g. movement and function, occurs as a result of recovery or compensation. Recovery relates to restoration or resolution of physiological and molecular changes, and also, from a clinical perspective, to functional improvement and/or return to usual activities of daily living[55]. These functional improvements may occur as a result of the adoption of compensatory movements. Compensatory movements of muscles, joints and body parts, which can occur on either the non-paretic or paretic side, is the use of alternative muscles to accomplish a task, that deviate from normal movement following stroke[56]. Compensatory movements are often encouraged to enable a quick resumption of some activities of daily living[57]. This, however, has the potential disadvantage of being associated with long-term problems such as reduced range of movement in joints, pain, further muscle weakness and phenomenon such as learned non-use[58]. This is an example of maladaptive neuroplasticity[35].

For someone with a severe stroke, compensatory movements may be the only means of gaining improvement in function. Severity of stroke also appears to affect where neural reorganization occurs[37]. In mild to moderate strokes, local reorganization is observed with new connections and sprouting in intact ipsilateral brain cells[37]. In more severe strokes, reorganisation is observed distant to the stroke contralaterally, with dendritic growth and pruning, and synapse formation[37]. This is because ipsilesional plasticity mechanisms are

limited due to extensive damage to the cortex. The site of cortical reorganisation may in turn affect the degree of recovery.

Predicting recovery

Clinically there remains uncertainty about the potential for recovery in all severity of strokes, raising questions as to why some people recover, and others do not[44]. The proportional recovery rule[59] suggests that amount of function regained is a proportion of the initial deficit. The rule suggests that, regardless of severity, within three months people will regain approximately 70% of function that had been lost on day three after stroke. However, the generalisability of this rule has been questioned as it has not been tested in people with severe stroke[60,61]. Furthermore, the rule is based on prediction of upper limb recovery that is heavily dependent on the integrity of the corticospinal tract.

Motor evoked potentials (MEPs) using transcranial magnetic stimulation (TMS) are non-invasive and widely used to test the integrity of the corticospinal tract. They have been deemed reliable predictors of upper limb recovery [62] although the presence of perilesional oedema and hyperexcitability within the cortex have been identified as factors that may negatively affect the accuracy of these tests[63]. However, the integrity of the corticospinal tract is not a strong determinant of walking[64] and the degree of lower limb motor recovery cannot be predicted by the magnitude of corticospinal MEP amplitude or the integrity of the corticospinal tract as ascertained by imaging, especially in people with severe or very severe stroke[62,65]. Given that some people with severe stroke return to walking but do not regain upper limb function, this suggests that the mechanisms involved are different. Jones et al., (2016) suggests that the

corticospinal tract has limited impact on walking and that sub-cortical structures such as the putamen, insula, brainstem and thalamus play a significant role in lower limb function and walking. Alternatively, walking and standing recovery may involve compensatory strategies such as over use of the non-paretic side.

There is a wealth of research predicting upper limb recovery[66-68]. However, much less in lower limb recovery[69] and a paucity of evidence in people with severe stroke. The ability to accurately predict functional recovery and outcome following stroke would enable realistic goal-setting, guide the type and duration of rehabilitation, and help to manage expectations[70]. Predictive data from neurophysiology and neuroimaging has been used in isolation and in combination with clinical variables (e.g. age, severity of muscle weakness), and clinical outcome measures[61,62,71]. However, there is no conclusive evidence to suggest one efficient, effective and accurate method of prediction following stroke.

1.4 Early mobilisation

Early mobilisation is the commencement of sitting out of bed, standing and walking training within 48 hours post-stroke[3,26]. There are several principles underpinning the rationale for early mobilisation. First, there is a wealth of evidence suggesting immobility has a detrimental impact on the neurological, musculoskeletal and cardiorespiratory systems (Sections 1.2 and 1.3)[18-20,22,24,25], which negatively affect recovery and functional outcome. Second, early after stroke in hospital, people are inactive and immobile for most of their day[72] despite supporting evidence that it is feasible for people to be more active, even for those with severe stroke[72]. Theoretically these common and serious complications can be prevented or minimised by early mobilisation[73,74].

Finally, the current concepts of biological recovery following stroke, suggest a critical period of opportunity for neuroplasticity and repair[75]. If the brain remodels itself based on experience[76], this supports practicing task-specific activities early after stroke to optimize recovery. These principles are supported by the National clinical guidelines[3,77] which therefore recommend early mobilisation after a stroke.

Despite evidence supporting early mobilisation, the outcomes of several randomised controlled trials (RCTs) have been mixed with concerns about its potential harms. For example, less favourable outcomes occurred when early mobilisation was instigated ≤24 hours post-stroke[78] compared to a reduction in complications when instigated ≥24 hours[79]. This finding is supported by other studies in which early mobilisation implemented ≥24 hours post-stroke was associated with increased independence in ADL and a faster return to walking[80]. However, heterogeneity of primary end-points makes direct comparison of effectiveness of early mobilisation interventions difficult.

Whilst early mobilisation is deemed to be safe ≥24 hours post-stroke[78-81], uncertainties have been identified with regards to dose (time in rehabilitation or number of repetitions[82]) and frequency. The AVERT Trial Collaborative Group suggest that shorter, more frequent mobilisation is preferable and this is reflected in the latest guidelines from the Royal College of Physicians[3] recommending patients accumulate at least 45 minutes daily. However, the main limitation of the RCTs is they did not specify time spent mobilising, intensity, frequency, or distinguish content of early mobilisation sessions in people with different severities of stroke. Therefore, it is possible that, other than transferring in and out of bed, no specialised equipment was used to facilitate standing for people with severe stroke. Further, active sitting was also

defined as a form of early mobilisation so people with a more severe stroke may have only participated in this activity with no opportunity to stand.

Opportunities to practice standing and sit to stand are important, because early training is associated positively with structural plasticity in animal models of stroke recovery. For example, after an ischemic cortical infarct, movement representation in the motor cortex was greater when training was initiated at one week rather than one month[83]. Findings in such animal studies and RCTs suggest that the ideal time to introduce task-skilled rehabilitative training to induce experience-dependent plasticity is early, but not immediately, after stroke. However, the exact time window for beneficial structural and functional outcomes remains unclear.

Despite the supporting evidence and clinical guidelines recommending early mobilisation, there is no evidence-based guidance as to how to implement early mobilisation specifically with people who have suffered a severe stroke. Arguably, these individuals are at the greatest risk of secondary changes because of their immobility. My personal experience of working in this area is that whilst there are regular opportunities for sitting people out of bed and facilitating them to undertake activities in lying and sitting, there is a lack of opportunity for regular standing and sit to standing practice early after stroke. The lack of opportunity to do so during the critical three-month post-stroke period, when maximal structural plasticity occurs, might negatively impact on functional outcome and quality of life.

1.5 Supported standing in people with stroke

Standing up early after a stroke is important, relevant and meaningful for people who have suffered a stroke. This was identified in discussions with people who

had suffered a stroke and their relatives when defining the research question and in the design of this feasibility trial. Patients reported that they believed the functional standing frame programme would “help me get back to normal”, “allow me to do things on my own” and for those of working age “help me get back to work”. Some participants cried when talking about being able to stand up, stating it is “really important to me”. Relatives of people with stroke commented that knowing their relative was practicing standing up was an “important milestone in their recovery”. Additionally, from a theoretical perspective, standing up and practising purposeful and meaningful activities of daily living have demonstrated to be important for adaptive plasticity.

People who have suffered a severe stroke have limited options and opportunities to stand up and are reliant on physical assistance and equipment. Supported standing devices such as a motorised standing frame allow people with severe stroke to attain and maintain a standing position through stabilising hips, knees and ankles with supports and/or straps[84]. Supported standing programmes have been commonly used as an adjunctive therapeutic intervention in clinical practice in people with neurological conditions such as multiple sclerosis and spinal cord injury[85]. Conversely supported standing programmes are not routinely used in sub-acute inpatient stroke rehabilitation[86] and standing frames have never been issued on patient’s discharge from SRUs in the South West of England where I have worked clinically.

Evidence from people with spinal cord injury, multiple sclerosis, stroke and traumatic brain injury indicates there are multiple benefits of supported standing. Stretching contracted muscles, decreasing spasticity, strengthening muscles, improving bladder and bowel function, relieving pressure areas,

reducing OH, improving bone strength[87-93] can be observed with 30 minutes of daily standing ranging from three to seven days per week.

Despite the aforementioned benefits of supported standing, currently there are no evidence-based guidelines for its use in adults with stroke or neurological conditions, and evidence on effectiveness has been identified as insufficient [85] and contradictory[94]. A positive trend for improvements in gross motor function and trunk control and a significant improvement in balance for individuals with stroke was observed following a standing intervention of 45 minutes of standing in addition to 45 minutes of usual physiotherapy in a RCT[95]. Conversely, a RCT of 14 consecutive 30-minute standing frame sessions found no difference in functional outcomes between groups in people with a sub-acute severe stroke[96]. The lack of functional improvement may be due to variation in the duration and intensity of treatment. Two systematic reviews highlighted the variation in duration and frequency of standing. Duration varied from 10 to 60 minutes and frequency of standing ranged from two to seven days per week with duration dependent on inpatient length of stay and participant recovery[84,85]. The lack of functional improvement may also be reflective of the heterogeneity and sensitivity of the various outcome measures used (Rivermead Mobility Index, Functional Independence Measure, Berg Balance Scale, Trunk Control Test, Barthel Index and Modified Ashworth Scale). Additionally, treatment was not standardised and was left to the therapists' discretion. A more recent RCT also failed to demonstrate any patient benefits above and beyond usual physiotherapy following 20 or 40 minutes of standing per day in people with sub-acute stroke[94]. Aside from dose and frequency, the passive element of the prolonged standing warrants acknowledgement. In these trials, participants undertook prolonged standing only and the addition of task-specific training,

such as repeated sit to stand may have resulted in greater improvement in functional outcomes.

1.6 Task-specific training

Task-specific training or repetitive task training, is based on the principle that in order to improve the performance of a particular task, that particular task needs to be practiced numerous times[97]. A meta-analysis demonstrated that if tasks were practised more intensively, (e.g. more repetitions), this resulted in improved recovery of ADL post-stroke[98]. Improvements were greater if the task had a functional goal[99]. Task-specific training combines both intensity of practice and functional relevance[97].

Sit to stand is one of the most frequently performed functional tasks of daily living and is an essential pre-requisite to walking[100]. The ability to stand up without assistance is also an important factor for independence in ADL[100] and falls prevention[101]. People with stroke commonly experience sensorimotor impairments which compromise their ability to sit to stand independently[101]. A Cochrane Review assessed the evidence of the effectiveness of therapy and training interventions aimed at improving the ability to sit to stand post-stroke. The review concluded that task-specific training to improve sit to stand is beneficial within stroke rehabilitation[102]. However, this moderate quality evidence included people who could already sit to stand independently after stroke. It is disappointing that people with severe stroke who are unable to sit to stand, stand or walk without mechanical and/or physical assistance were not included or acknowledged in this systematic review. People with severe stroke are arguably at the greatest risk of secondary neuromuscular complications and

are possibly being denied the opportunity to explore the potential benefits of this aspect of task-specific training.

It has been suggested that the search continues for new therapies that can be widely incorporated into clinical practice to treat people with stroke[103]. There is also a need to rigorously test existing clinical practice with specific patient populations (e.g. people with severe stroke) at optimal times (e.g. during the critical sub-acute period) to make meaningful recommendations for current and future clinical practice. The Cochrane Review 'Interventions for improving sit-to-stand ability following stroke'[102] clearly demonstrates that task-specific training with sit to stand has not been adequately evaluated in people with severe stroke. This is the rationale for incorporating task-specific training (repeated sit to stand) into the functional standing frame programme that is being evaluated in this feasibility trial.

The functional standing frame programme will combine two physiotherapy interventions that have separately been evaluated and reported in the literature: prolonged standing and repeated sit to stand. Given that sit to stand and standing are functionally linked tasks as well as common functional tasks, it is surprising that their combined effects have not been previously tested in stroke. Therefore, development and evaluation of this novel combination of interventions in people with severe stroke is warranted.

A significant limitation of task-specific training and early mobilisation in people with severe stroke is orthostatic hypotension (OH). It can be a barrier to rehabilitation and can contribute to increased morbidity and disability and thus also warrants being addressed.

1.7 Orthostatic hypotension

OH is defined by consensus as a sustained drop in systolic blood pressure of at least 20 mmHg and/or diastolic blood pressure of at least 10 mmHg within 3 minutes of moving from supine to standing or following head-up tilt to at least 60 degrees[104,105].

Orthostatic hypotension is associated with ischemic stroke and can affect rehabilitation outcomes [106-108]. Prevalence of OH varies from 10%[109] to 52.1%[108] during acute- and sub-acute stroke rehabilitation hospitalisation. A reason for the variation in prevalence may be due to the severity of stroke for people included in studies. Participants in the study by Kong & Chuo (2003) had predominantly severe strokes who were more likely to suffer from immobility, which is a predisposing factor for OH, which may account for the high prevalence in this study.

Immobility or bed rest has a negative impact on the cardiovascular system[110]. Adequate functioning of the cardiovascular system in everyday physical activity is highly dependent on exposure to gravitational stress that naturally accompanies an upright standing position[111]. During bed rest, the cardiovascular system quickly (two to four days) adapts[112]. Once bed rest is discontinued, however, the cardiovascular system has difficulty reversing this adaptation. Its compensatory mechanisms fail to adequately increase cardiac output and the person experiences OH; a hallmark of bed rest deconditioning[112]. However, these studies were conducted in healthy individuals, and people with stroke, especially severe stroke may likely have muscle weakness which may impede the ability of their lower limb and abdominal muscles to prevent blood pooling.

The presence of OH can interfere with and limit rehabilitation, especially in stroke where mobilisation (out-of-bed activities such as sitting, standing and walking) is recommended at the earliest opportunity[3]. The goal of treating OH is to raise a person's standing blood pressure without also raising their resting blood pressure, specifically to reduce OH symptoms, increase the time they can stand and improve their ability to perform ADLs. Being able to treat OH effectively and efficiently to minimise any disruptions to rehabilitation is of paramount importance. Knowledge about the most effective manner in which to achieve this is the rationale for undertaking the systematic review, reported in Chapter 2.

1.8 Research considerations

Rehabilitation interventions in stroke are predominately considered complex interventions, as they typically comprise several interacting components[113]. For example, the functional standing frame programme depends on behaviours required by those delivering and receiving the intervention and the surrounding organisational culture. The intervention also has multiple outcomes (e.g. function, physical disability, psychological wellbeing and quality of life). It is vital that complex interventions are evaluated, and this frequently requires an assessment of the feasibility of delivering a clinical trial. This feasibility trial asks whether the functional standing frame programme can be delivered as part of an RCT to people with severe stroke at a specific time and within the NHS SRU setting. A process evaluation of the feasibility trial enabled the multifaceted and interacting components to be evaluated to establish clinical feasibility, acceptability and compliance. A process evaluation aims to examine factors such as how interventions are implemented, how participants respond to interventions and change their behaviour (or not), and contextual factors which

affect different stages of the intervention[114]. The Medical Research Council framework[115] (Figure 1.1) was used in this feasibility trial, which includes both qualitative and quantitative methods.

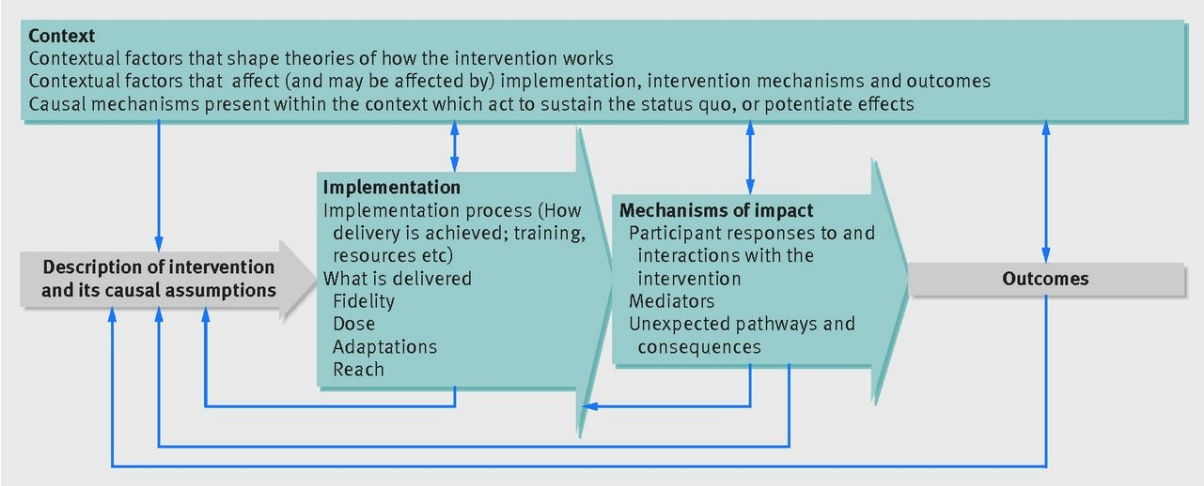


Figure 1.1 Medical Research Council Framework

This framework was used as a modelling process to inform feasibility for a larger, future RCT. A pragmatic and iterative approach was used to answer a question relevant to people with severe stroke. Furthermore, the framework enabled unknown aspects of the trial such as acceptability, feasibility and recruitment to be identified, so that weaknesses could be addressed in a subsequent main trial.

An important aspect of the process evaluation and overall assessment of feasibility involved stakeholder perspectives. Stakeholders are individuals or groups responsible for or affected by health- and healthcare-related decisions[116]. Perspectives of trial participants, their relatives and physiotherapists delivering the intervention and recruiting participants were considered critical to understanding the feasibility of this trial and providing valuable insights into the design and delivery of a subsequent main trial. Their involvement is expanded on in Chapter 3, methodology.

1.9 Summary

Clinical experience and discussions with people who have had a severe stroke have highlighted their priorities and goals to “stand up early after stroke”. This is aligned with current national clinical guidelines but is not standard clinical practice for people with severe stroke.

Stroke has a devastating impact on people’s lives, severely affecting their ability to be independent in ADL. People who have suffered a severe stroke are immobile and although the immobility is primarily caused by neurological damage, it can be worsened by bed rest and sedentary behaviour. This can have a detrimental impact on neurological, musculoskeletal and cardiorespiratory systems (including blood pressure) and further impede functional ability and reduce quality of life. Harmful changes in these systems can theoretically be prevented or minimised by early mobilisation, specifically standing up early after stroke. One factor that may limit standing time in severe stroke is OH. The impact of OH on standing for people who have suffered a stroke has been identified in this chapter and provides the rationale for the systematic review of non-pharmacological interventions to treat OH, presented in Chapter 2.

Standing practice using a standing frame is commonly used with people with neurological conditions but not routinely in sub-acute stroke rehabilitation. This is aligned with current clinical practice in Cornwall and Devon (location of the feasibility trial), where standing practice as part of sub-acute inpatient rehabilitation for people with a severe stroke varies. Evidence on the effectiveness of supported standing for people with stroke has been identified as insufficient and contradictory. Conversely, the evidence for task-specific

training, (e.g. repeated sit to stand) has reported functional benefits when compared to usual care. Existing rehabilitation interventions/practices have not been appropriately and rigorously tested with people with severe stroke; this underpins the rationale for this feasibility trial.

Standing and sit to stand are important functionally linked tasks, and currently it is not known whether this novel combination of physiotherapy interventions for people with severe stroke is effective in everyday clinical practice. These two interventions were combined to create a functional standing frame programme. This is my original contribution to the existing knowledge-base for the rehabilitation of people who have had a severe stroke. The functional standing frame programme addresses a key concern for people who have suffered a severe stroke. However, several uncertainties exist which need to be understood prior to progressing to a full-scale RCT, including acceptability and tolerance of the intervention and practicality of the trial procedures. This feasibility trial will provide important insights to resolve these uncertainties and enable a protocol to be finalised for use in an anticipated definitive trial.

1.10 Thesis aim and structure

This thesis aims to determine the feasibility of undertaking a RCT to evaluate the effectiveness of a functional standing frame programme for people with severe stroke during their inpatient sub-acute rehabilitation, using a feasibility RCT and nested qualitative component. In my role as a researcher and practising physiotherapist, my intention is to ensure that this research is clinically relevant and meaningful to people with severe stroke. This thesis is derived from, and informed by, patients, their families, clinicians, methodologists and public involvement.

This chapter has provided an introduction and background to the feasibility trial, identifying why this research is warranted. Chapter 2 presents a systematic review that summarizes the best available evidence regarding the effectiveness of non-pharmacological interventions to treat OH in people with stroke. Chapter 3 presents the research methodology with justification of the trial design of a randomised controlled feasibility trial and nested qualitative component. Chapter 4 presents the results in two parts: Part A: the quantitative results from the intervention and control group sessions, baseline and follow-up assessments; Part B the qualitative data from the interviews and focus group. The final chapter discusses all data and addresses the feasibility objectives, providing conclusions and recommendations for future research.

Chapter 2 Systematic review

2.1 Introduction

Orthostatic hypotension (OH) is common in people with stroke and can interfere with and limit rehabilitation, especially in sub-acute rehabilitation where early mobilisation is recommended. Stroke is common, although not exclusive, to elderly people, with the majority (59%) of strokes occurring in people over 65 years of age. However, nearly one third (31%) of strokes occur in people aged 50-69 years of age. The prevalence of OH in elderly people is high, both in the United Kingdom and internationally, and higher in elderly people who are hospitalised than those living in the community. Elderly people and people with stroke are more likely to have multimorbidity[117] and thus are at risk of polypharmacy (taking at least five medications)[118]. Therefore, identifying non-pharmacological interventions to treat OH in people with stroke and elderly people is of paramount importance to minimise any disruptions to rehabilitation.

This chapter presents a summary of the best available evidence regarding the effectiveness of non-pharmacological interventions to treat OH in people with stroke. The findings informed the development of the intervention to ensure OH was assessed and treated effectively, ensure the intervention was reflective of clinical practice and optimise recruitment.

2.2 Background and rationale

Orthostatic hypotension is a common clinical phenomenon in elderly people, people with stroke and other neurological conditions[108,119-121]. It is defined by consensus as a sustained drop in systolic blood pressure (sBP) of at least 20 mmHg and/or diastolic BP (dBP) of at least 10 mmHg within three minutes of

moving from supine to standing or following head-up tilt to at least 60 degrees[105,122].

Orthostatic hypotension has both non-neurogenic and neurogenic causes and can be acute or chronic[6.] Non-neurogenic causes fall into three categories: hypovolemia (reduced blood volume), cardiac pump failure and venous pooling. Neurogenic OH is associated with neurological diseases and can be caused by abnormalities in either the central nervous system (e.g. stroke, spinal cord injury or Parkinson's disease) or peripheral nervous system (e.g. Guillain Barre´ syndrome or diabetic neuropathy)[123].

A variety of symptoms are caused by OH which is a frequent cause of syncope (transient loss of consciousness, rapid onset and short duration) that may contribute to morbidity, disability and even death.[105] Other characteristic symptoms include: (a) dizziness/light headedness and pre-syncope; (b) weakness, fatigue and lethargy; (c) palpitations and sweating; (d) visual disturbances; (e) hearing disturbances; and (f) neck, shoulder and low back pain[124,125]. These symptoms relate to the degree of the fall in blood pressure (BP) and hypoperfusion (reduced blood flow) of the brain and other organs and can vary in severity.

The prevalence of OH in older people (defined for this review as aged 50 years and over[126]) is high, both in the UK and internationally, but variable depending on the characteristics of the population studied. It is more common in elderly people who are hospitalised and institutionalised (up to 68%)[127] than in those living in the community (30%)[128]; likely a reflection of the presence of multiple disease processes in the former group. In addition, orthostatic changes in BP become more exaggerated after prolonged immobilisation[110]. Orthostatic

hypotension is common in people with stroke[129], occurring in up to 52%[108]. It is common in other neurological conditions and occurring in approximately 40%[120] of people with Parkinson's disease and 50–82% of people with spinal cord injury, depending on the level of lesion[121]. Given that stroke is predominately but not exclusively, seen in elderly people, it is possible that the prevalence of OH post-stroke may be much higher. This aligns with current European guidelines that highlight OH is underdiagnosed[105]. The inclusion of older people, stroke and other neurological conditions in this systematic review is justified for two reasons. Firstly, the limited number of studies available that are specific to stroke, and secondly because there are overlaps in its mechanism of causation and presentation amongst these populations. The presence of OH can interfere with and limit rehabilitation, especially in stroke where early mobilisation is recommended at the earliest opportunity[3]. Early mobilisation has demonstrated improved functional outcomes[79] however, early mobilisation studies for people with acute stroke excluded people from the intervention arm if they had OH on three consecutive occasions[81,94]. Given the high incidence of OH in this population such exclusion criterion could impact on recruitment rates and generalisability of the findings of early mobilisation intervention trials influencing the number of people potentially benefitting from these interventions.

The risk of harm with OH must be acknowledged and addressed. In acute and sub-acute stroke, OH has the potential to cause further brain damage, both in the area surrounding the stroke (penumbra), and throughout the brain, due to hypoperfusion, a consequence of impaired cerebral autoregulation.[130] This may result in increased disability and mortality. Given this risk of harm, it is surprising that current guidelines for the management of people with stroke[3,131,132] do not provide guidance on managing OH.

The goal of managing OH is to raise the patient's standing BP without also raising their resting BP, and specifically to reduce OH symptoms, increase the time they can stand and improve ADLs performance[133]. Currently, there is no specific intervention that achieves all these goals, despite the multitude of pharmacological and non-pharmacological interventions available. A recent systematic review highlighted that although there were multiple pharmacological interventions available in the UK, Europe and United States of America (USA), there is little high-quality data as to which is the best[134]. The burden of pharmacological interventions warrants consideration. People with stroke and elderly people are more likely to have multimorbidity[117], thus are at risk of polypharmacy[118]. Therefore, identifying non-pharmacological interventions to treat OH in these populations is of paramount importance.

Reviews[135] and guidelines[105,136] from the USA and Europe for the management of OH recommend non-pharmacological interventions as the first line approach before progressing to pharmacological interventions. However, people with stroke often have complex needs and severe disability, thus some non-pharmacological interventions may not be appropriate. For example, undertaking physical manoeuvres such as squatting and leg crossing require a specific level of mobility and balance, and functional electrical simulation may be contraindicated due to other medical conditions or skin frailty. Therefore, these guideline recommendations cannot be automatically translated to people with stroke, which underpins the rationale for this review. Identifying non-pharmacological interventions to treat OH in people with neurological conditions has been highlighted as a research priority[85,137].

An initial search of the literature – MEDLINE, Embase, CINAHL, Cochrane Database and PROSPERO – identified one systematic review examining studies that evaluated non-pharmacological interventions to treat OH[138]. However, this review was broad, covering various patient populations and not restricted to people with stroke or other neurological conditions, or elderly people. Furthermore, the review did not focus on any specific outcomes such as impact on mobilisation or functional ability. The initial search also identified a paucity of evidence for non-pharmacological interventions to treat people with stroke. Thus, this systematic review included people with other neurological conditions such as Parkinson's disease and spinal cord injury. The systematic review will allow the development of a protocol to implement into the feasibility trial of the functional standing frame programme.

2.3 Review question

What is the evidence base for non-pharmacological interventions in treating OH in elderly people and people with a neurological condition?

2.4 Review objectives

The objectives of the review are to determine the effectiveness of non-pharmacological interventions for OH in elderly people and people with a neurological condition in terms of:

- OH, resting BP and cerebral blood flow
- mobilization (especially standing); engagement in activities of daily living and/or participation in rehabilitation programs

2.5 Inclusion criteria

2.5.1 Participants

The current review considered studies that included participants diagnosed with OH by a medical professional using criteria such as the International Classification of Diseases and Related Health Problems (ICD-10)[139]. Participants were included if they were aged 50 years and over to represent the elderly population. Currently, there is no agreed definition of “elderly” ‘‘older’’ or ‘‘old people’’, with 50 years accepted as the definition of older people based on the World Health Organization Older Adult Health and Ageing in Africa project[126]; this was used for the purposes of this review. In addition, participants aged 18 years and over with either a progressive or sudden, non-progressive neurological condition of the central nervous system were included. Peripheral nervous system conditions were excluded.

Participants receiving treatment for acute or chronic OH were included, which encompassed treatment carried out in hospitals, outpatient clinics, in-patient rehabilitation units and the community (either in their own homes or in a residential or nursing home setting).

2.5.2 Interventions

The review considered studies that evaluated non-pharmacological interventions to treat OH. These included compression garments (e.g. lower limb compression stockings or abdominal corset); neuromuscular stimulation; physical manoeuvres (e.g. squatting and bending at the waist) and isometric exercises for arms, lower limbs and abdominal muscles during standing; raising head of bed at night time or increasing fluid and salt intake. However, a full systematic search identified additional interventions that were considered (e.g.

frequency and size of meals). Interventions of any duration, frequency or intensity were considered.

2.5.3 Comparator

The review considered studies that compared the non-pharmacological interventions listed above with no intervention, pharmacological interventions and/or other non-pharmacological interventions.

2.5.4 Outcomes

Outcomes considered included: sBP, dBP (both lying and standing using manual or automated device), time to symptoms and time to recovery; resting heart rate (HR) (assessed using a manual or automatic device); cerebral blood flow (assessed using transcranial Doppler or correlation spectroscopy etc.); observed and/or perceived symptoms; duration of standing or sitting in minutes; tolerance of therapy (e.g. ability to participate in therapy measured in length and frequency of sessions); function/ADL and adverse events/effects where this information was provided.

2.5.5 Types of studies

This review considered experimental and epidemiological study designs including RCTs, non-RCTs, quasi-experimental, before and after studies, prospective and retrospective cohort studies case-control studies and analytical cross-sectional studies. In addition, descriptive epidemiological study designs including case series, individual case reports and descriptive cross-sectional studies were also considered.

2.6 Methods

This systematic review was conducted in accordance with the Joanna Briggs Institute (JBI) methodology for systematic review of effectiveness[140] and, according to an *a priori* published protocol[141].

2.7 Search Strategy

The search strategy was carried out in January 2017 and updated in April 2018 and aimed to find both published and unpublished studies. A three-step search strategy was utilized. An initial limited search of MEDLINE, AMED, CINAHL and Embase was undertaken, followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the articles. A second search using all identified keywords and index terms was then undertaken across all included databases. The key terms were: stroke, cerebrovascular accident, CVA, upper motor neuron disorder, neurological, Parkinson's Disease, Multiple Sclerosis, spinal cord injury, non-pharmacological, compression, bandages, splint, abdominal, legs, lower limbs, orthostatic hypotension, postural hypotension, orthostasis, low BP, autonomic dysfunction, vascular response, cerebral blood flow, function, functional outcome, activities of daily living, quality of life. Third, the reference list of all studies that met the inclusion criteria and articles were searched for additional studies. The search was restricted to studies published in English as team members were unable to translate other languages. There were no date limiters. Databases that were searched included: MEDLINE (Ovid), Embase (Ovid), The Cochrane Central Register of Controlled Trials, CINAHL, AMED (EBSCO), PEDro, http://clinicaltrials.gov and OpenGrey. A search for unpublished studies was conducted in Google Scholar, Conference Papers Index. Appendix 1 provides an example of the search strategy used in all databases.

2.8 Study selection

Following the search, all identified citations were loaded into EndNote bibliographic software[142] and duplicates removed. Titles and abstracts were screened by two independent reviewers for assessment against the inclusion criteria for the review. The full text of potentially eligible studies was retrieved and assessed in detail against the inclusion criteria by two independent reviewers. The details of studies that met the inclusion criteria were imported into the Joanna Briggs Institute's System for the Unified Management, Assessment and Review of Information (JBI SUMARI)[143] and JBI Critical Appraisal Checklist for Randomized Controlled Trial, Quasi-Experimental Studies, Case Control Study, Case Reports were used to critically appraise included studies depending on the study design. Full text studies that did not meet the inclusion criteria were excluded and reasons for their exclusion are provided in Appendix 2. Any disagreements that arose between the independent reviewers were resolved through discussion, or with a third reviewer.

2.9 Assessment of methodological quality

Selected studies were critically appraised by two independent reviewers for methodological quality using the standardized critical appraisal instruments from the JBI. Disagreements were resolved through discussions, negating the requirement for a third reviewer.

2.10 Data extraction

Quantitative data were extracted from papers using the standardized data extraction tool available in JBI SUMARI[144] by two independent reviewers. The

data extracted included specific details about the interventions, populations, study methods, outcomes of significance and specific objectives.

Authors of papers were contacted to request missing or additional data where required. Thirteen authors were contacted. Responses were received from five.

2.11 Data synthesis

Due to the variability and heterogeneity in the parameters of the papers presented, it was not possible to include all papers in the meta-analyses. For papers not included in the meta-analyses, data are presented as mean +/- SD unless otherwise stated, alongside the narrative summary.

Outcomes for papers included in the meta-analyses were: the change in mean arterial BP between supine and maximum upright stand or tilt (depending on what the studies measured) at the earliest measurement point (e.g. selecting measurements at one minute rather than two minutes if both available). Where mean arterial pressure (MAP) was not available it was calculated with constant proportions between dBP and sBP blood pressures: MAP = 1/3 sBP + 2/3 dBP (mmHg).[145] Where dBP data was not available, the change in sBP was used.

Results, where possible, were pooled in statistical meta-analysis using JBI SUMARI. Effect sizes are expressed as standardized mean differences and their 95% confidence intervals calculated for analysis. Heterogeneity was assessed statistically using the standard chi-squared and I squared tests. The choice of random effects model, and methods for meta-analysis were based on the guidance by Tufunaru et al. 2015[146]. There were insufficient individualized data to conduct subgroup analyses[144], and insufficient number of studies to generate a funnel plot[147].

2.12 Assessing confidence

A 'Summary of findings' table (Appendix 3) was created using GRADEPro GDT software for all studies included in the meta-analysis. The GRADE approach for grading the quality of evidence was followed. The 'Summary of Findings' table presents the following information where appropriate: absolute risks for treatment and control, estimates of relative risk, and a ranking of the quality of the evidence based on study limitations (risk of bias), indirectness, inconsistency, imprecision and publication bias[148-151]. Outcomes included in the 'Summary of findings' table:

Mean arterial blood pressure and systolic blood pressure.

2.13 Results

2.13.1 Study inclusion

The results of the search and study selection process are presented in Figure 2.1. A total of 4,481 potentially relevant studies were identified. Of those, 1,080 were duplicates. From the remaining 3,401 records, 3,316 were excluded after title and abstract assessment. The eligibility of 85 full-text articles were assessed, 34 of which were excluded. The methodological quality of the remaining 51 studies were assessed. From those 51 studies, 13 were randomised control trials, 34 quasi-experimental, one case control study and three were case report studies. Eight studies were excluded. The reasons for study exclusion are detailed in Appendix 2.

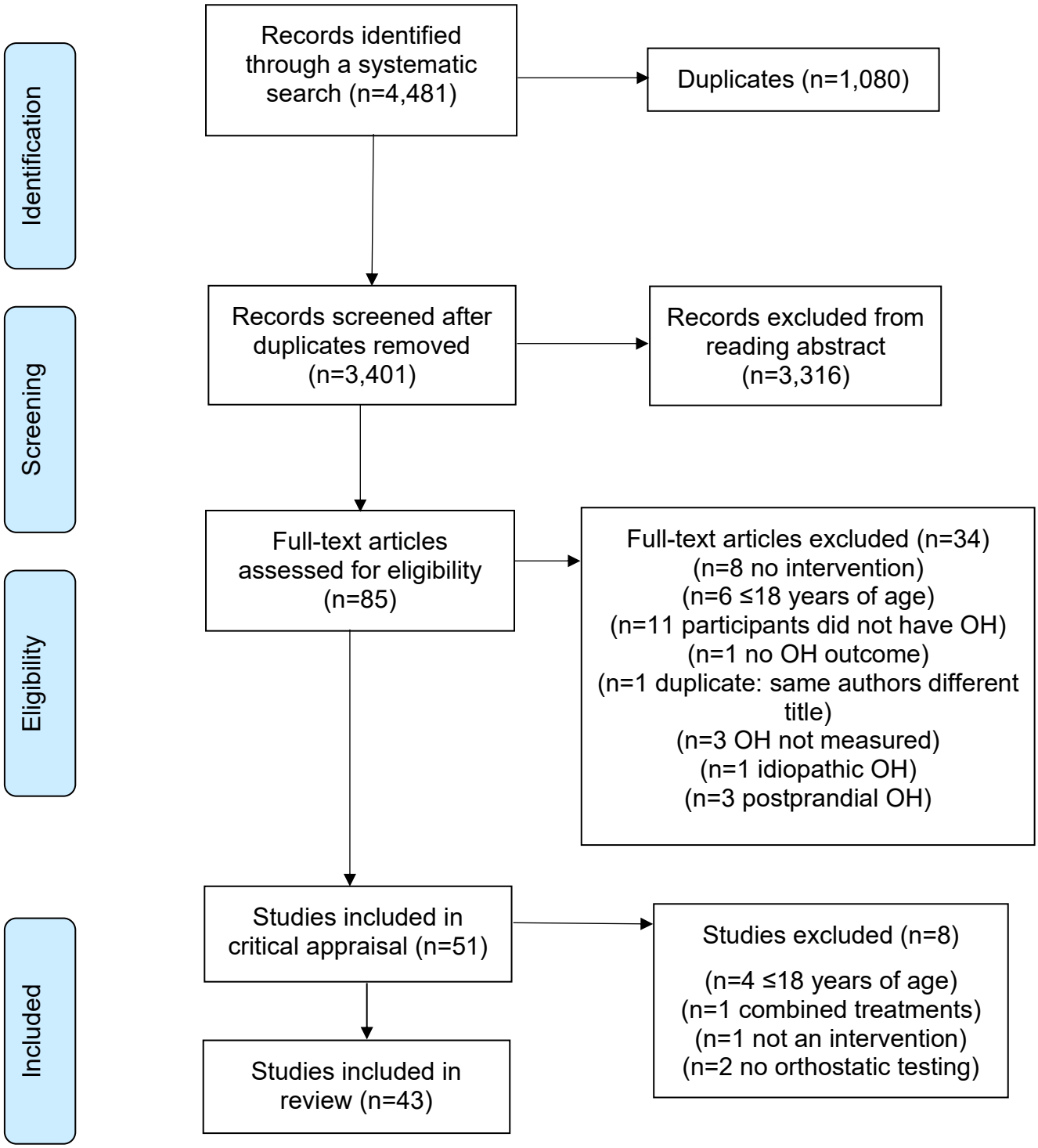


Figure 2.1 PRISMA Flowchart of the study selection and inclusion process

2.13.2 Methodological quality

Methodological quality of the studies was not addressed until the final selection of studies had been made for this systematic review. Methodological quality of individual studies was critically appraised using JBI's instruments and included in the study analysis. Methodological quality in all studies varied.

During the process of assessing methodological quality, eight studies were deemed ineligible and not included in the review. One study had combined treatments and the effect of a given intervention was not clear. Seven other studies did not meet the inclusion criteria. All seven studies are marked with an Asterix and reasons for excluding the eight studies are detailed in Appendix 2.

Table 2.1 presents the critical appraisal of the 13 RCTs included in the systematic review. True randomization was not used in one study, unclear in six and used in six studies. Concealed allocation to treatment was used in five studies and unclear in four studies. Blinding of participants and of those delivering the intervention and outcome assessors were low in most studies. Follow-up was either complete, or strategies to address incomplete follow-up were utilized in nine studies, and eight studies analysed participants in the groups to which they were randomised.

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13
Faghri & Yount[152]	N	N	N	N	N	N	Y	N	Y	Y	Y	Y	N
Fan et al[153]	U	U	Y	N	U	U	Y	N	Y	Y	Y	Y	N
Fanciulli et al[154]	U	N	Y	U	N	N	Y	Y	U	Y	Y	Y	Y
Figueroa et al[155]	U	U	Y	N	N	U	Y	Y	N	Y	Y	Y	Y
Kanegusuku[156]	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y
Gorelik et al[157]	U	U	Y	N	N	U	Y	Y	U	Y	Y	Y	Y
Luther et al[158]	Y	N	Y	N	N	N	Y	N	Y	Y	Y	Y	Y
Phillips et al[159]	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Podoleanu et al[160]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y
Rocca et al[161]	Y	Y	N	N	N	U	Y	Y	Y	Y	Y	Y	Y
Takahagi et al[162]	U	U	Y	N	U	U	Y	Y	Y	Y	Y	Y	Y
Taveggia et al[163]	Y	N	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y
Vijayakumar et al[164]	U	Y	Y	U	U	U	Y	U	U	Y	U	Y	Y
Total %	**46.2**	**38.5**	**76.9**	**15.4**	**7.7**	**7.7**	**100**	**69.2**	**69.2**	**100**	**92.3**	**100**	**84.6**

Y = Yes, N = No, U = Unclear; JBI critical appraisal checklist for randomised controlled trials: Q1 = Was true randomization used for assignment of participants to treatment groups?; Q2 = Was allocation to treatment groups concealed?; Q3 = Were treatment groups similar at baseline?; Q4 = Were participants blind to treatment assignment?; Q5 = Were those delivering treatment blind to treatment assignment?; Q6 = Were outcome assessors blind to treatment assignment?; Q7 = Were treatment groups treated identically other than the intervention of interest?; Q8 = Was follow-up complete, and if not, were strategies to address incomplete follow-up utilized?; Q9 = Were participants analysed in the groups to which they were randomised?; Q10 = Were outcomes measured in the same way for treatment groups?; Q11 = Were outcomes measured in a reliable way?; Q12 = Was appropriate statistical analysis used?; Q13 = Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Table 2.1 Critical appraisal of methodological quality results of eligible randomised controlled trials

Table 2.2 presents the results of the critical appraisal of methodological quality of eligible quasi-experimental studies. Cause and effect was clear in all but two studies. In five studies, Q2 and Q3 were not applicable because there were no comparisons made. There was no control group in 13 of the 34 studies. In two studies, Q6 was not applicable because one was not an intervention study and subsequently excluded (Sasaki), in the other study all tests were completed on the same day and therefore there was no follow-up period. Q7 was deemed not applicable to one study because no comparisons were made.

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Bouvette et al[165]	N	N	N	N	Y	Y	U	U	Y
Brilla et al[166]	Y	N/A	N/A	N	Y	Y	Y	Y	Y
Chao & Cheing*[167]	Y	Y	Y	N	Y	Y	Y	Y	Y
Denq et al[168]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Elokda et al[169]	Y	Y	Y	Y	Y	N	Y	Y	Y
Faghri & Yount[170]	Y	Y	Y	Y	Y	N	Y	Y	Y
Gorelik et al[171]	Y	U	U	Y	Y	Y	Y	Y	Y
Gorelik et al[172]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Hamzaid et al[173]	Y	N/A	N/A	N	Y	Y	Y	Y	Y
Henry et al[174]	Y	N/A	N/A	N	N	U	Y	Y	U
Hilz et al*[175]	Y	Y	U	Y	Y	Y	Y	Y	Y
Hohler et al*[176]	N	Y	N	N	Y	N	Y	U	Y
Huang et al*[177]	Y	Y	Y	N	Y	U	Y	Y	Y
Humm et al[178]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Kuznetsov et al[179]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Loew et al[180]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Lopes et al[181]	Y	Y	U	Y	Y	Y	Y	Y	Y
Lucas et al[182]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Mader[183]	Y	Y	Y	Y	Y	Y	Y	Y	Y

Puvi-Rajasingham & Mathias[184]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Rimaud et al[185]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Sampson*[186]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Sasaki et al*[187]	Y	Y	Y	N	Y	N/A	Y	Y	Y
Shannon et al[188]	Y	Y	Y	N	Y	Y	Y	Y	Y
Smit[189]	Y	Y	Y	N	Y	N/A	Y	Y	Y
Smit[190]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ten Harkel et al[191]	Y	Y	Y	Y	Y	Y	Y	N	Y
Ten Harkel et al[192]	Y	Y	U	N	Y	Y	Y	Y	Y
Tutaj et al[193]	Y	N/A	N/A	N	N	Y	Y	Y	Y
van Lieshout et al[194]	Y	Y	N	Y	Y	Y	Y	U	Y
Wadsworth et al[195]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Yoshida et al[196]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Young & Mathias[197]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Zion et al[198]	Y	N/A	N/A	N	Y	Y	N/A	Y	Y
Total %	**94.1**	**79.4**	**64.7**	**61.8**	**94.1**	**79.4**	**94.1**	**88.2**	**97.1**

Y = Yes, N = No, U = Unclear, N/A – not applicable; JBI critical appraisal checklist for quasi-experimental studies; Q1 = Is it clear in the study what is the 'cause' and what is the 'effect' (i.e., there is no confusion about which variable comes first)?; Q2 = Were the participants included in any comparisons similar?; Q3 = Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?; Q4 = Was there a control group?; Q5 = Were there multiple measurements of the outcome both pre and post the intervention/exposure?; Q6 = Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?; Q7 = Were the outcomes of participants included in any comparisons measured in the same way?; Q8 = Were outcomes measured in a reliable way?; Q9 = Was appropriate statistical analysis used?

*studies excluded during critical appraisal process

Table 2.2 Critical appraisal of methodological quality results of eligible quasi-experimental studies

Table 2.3 presents the critical appraisal results for eligible case report studies. The patient's history was not clearly described or presented as a timeline for two of the three studies. Diagnostic tests or assessments, and the interventions or procedures were described in two of the three studies. Adverse events were reported in two of the three studies.

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Helmi[199]	Y	Y	Y	Y	N	Y	Y	Y
Mikula et al*[200]	Y	N	Y	N	Y	Y	N	Y
Taylor et al*[201]	Y	N	Y	Y	Y	Y	Y	Y
Total %	**100**	**33.3**	**100**	**66.7**	**66.7**	**100**	**66.7**	**100**

Y = Yes, N = No, U = Unclear; JBI critical appraisal checklist for case report studies; Q1 = Were patient's demographic characteristics clearly described?; Q2 = Was the patient's history clearly described and presented as a timeline?' Q3 = Was the current clinical condition of the patient on presentation clearly described?; Q4 = Were diagnostic tests or assessment methods and the results clearly described?; Q5 = Was the intervention(s) or treatment procedure(s) clearly described?; Q6 = Was the post-intervention clinical condition clearly described?; Q7 = Were adverse events (harms) or unanticipated events identified and described?; Q8 = Does the case report provide takeaway lessons?

*studies excluded during critical appraisal process

Table 2.3 Critical appraisal of methodological quality results of eligible case report studies

Confounding factors were not identified in the case control study. All other aspects of methodological quality were met as presented in Table 2.4.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Galizia et al[202]	Y	Y	Y	Y	Y	N	N	Y	Y	Y
Total %	**100**	**100**	**100**	**100**	**100**	**0.0**	**0.0**	**100**	**100**	**100**

Y = Yes, N = No, U = Unclear; JBI critical appraisal checklist for case control study; Q1 = Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?; Q2 =Were cases and controls matched appropriately?; Q3 = Were the same criteria used for identification of cases and controls?; Q4 = Was exposure measured in a standard, valid and reliable way?; Q5 = Was exposure measured in the same way for cases and controls?; Q6 = Were confounding factors identified?; Q7 = Were strategies to deal with confounding factors stated?; Q8 = Were outcomes assessed in a standard, valid and reliable way for cases and controls?; Q9 = Was the exposure period of interest long enough to be meaningful?; Q10 = Was appropriate statistical analysis used?

Table 2.4 Critical appraisal results of eligible case control study

2.13.3 Characteristics of included studies

Date of publication ranged from 1984 to 2018, and all were published in English. In the sections below the main features of these studies are summarized. Detailed information about the setting, participants, methods, interventions, outcomes and results are provided in Appendix 4.

2.14 Review findings

2.14.1 Study settings

Nineteen of the included studies were undertaken in Europe (four in the UK[,174,184,178,197], six in the Netherlands[203,204,192,189,191,194,], three in Italy[205,206,160], two in Germany[158,188], one in Austria[154], one in France[185], two in Switzerland[161,180]). Of the remaining 24 studies, 10 were undertaken in the USA[152,155,165,166,169,170,181,183,198,207], three in Israel[157,171,172], two in Canada[159,196], two in Brazil[162,208], one in India[164], one in Malaysia[173], one in Russia[179], one in New Zealand[182], one in Australia[195] and it was unclear in which country two studies were undertaken.[193,209].

The interventions described were undertaken in: hospital inpatient settings[157,171,172,180,184,195,197,204,210], rehabilitation facilities[152,164,169,170,173,185,206], outpatient clinics or centers[162,174,196,211,212], laboratories[154,155,165,178,182,203,213], medical centers[175,181,191,214], neuro rehabilitation units[158,205], a stroke rehabilitation unit[179], an autonomic dysfunction center[188], a hospital clinic[160], a research center[183], or community settings.[156,166,173,209] Two studies did not report where they were undertaken[193,207].

2.14.2 Participants

The 43 studies analysed included a total of 1,084 participants, ranging in sample size from one (case report study[204]) to 128 (quasi-experimental study[179]). The age range of participants was reported in 20 studies[154,155,169,173,174,183-185,191,195,196,203,204,207,210-215], and was from 18 to 89 years. Twenty-four studies[152,157,158,160,162,164-166,170-172,178-182,193,195,197,205,206,208-210] reported mean age. One study reported the age range for participants with

autonomic failure, and mean age for nine participants with idiopathic OH[188]. There was a total of 440 elderly (≥50 years) participants.

Gender was reported for the intervention group in all studies. In total, there were 525 male participants (48%). Six studies included only male[169,173,181,182,185,204], 16 studies included more males than females, two studies had an equal number of males and females[182,191], three studies did not report gender for controls[152,170,211].

Studies included participants with OH (n=484), stroke (n=170), spinal cord injury (n=86), Parkinson's disease (n=55), brain injury (n=28), brain haemorrhage (n=18), syncope (n=21), familial dysautonomia (n=17), cardiac arrhythmias (n=10), dizziness/palpitations (n=27), infectious diseases (n=21), pulmonary oedema (n=10), acute coronary syndrome (n=11), decompensated heart failure (n=18), other (n=8) and healthy controls (n=100); with four of the 1,084 participants having both spinal cord injury and OH, and others having multiple conditions.

Inclusion criteria for studies varied. Fourteen studies had OH as an inclusion criterion. Nine studies defined OH as a decrease in sBP of >20mmHg or decrease in dBP >10mmHg after a change in posture[154,157,164,166,171-173,206,209,213]. Other definitions were decrease in sBP >30mmHg or decrease in dBP >15mmHg[155]; sBP fall by at least 40mmHg or dBP fall by at least 30mmHg[193]; a decrease in sBP of >30mmHg or decrease in dBP >20mmHg[207], and progressive decrease in BP below a value of 90mmHg[160]. Eleven studies had OH as an inclusion criterion but did not provide a definition of OH[165,174,178,184,188,191,197,203,211,212,214]. Twelve studies had inclusion criteria of elderly people: ≥50[208], ≥60[171,172,209,213] or ≥65[157,180,206] years or specified an age

range[166](60-85 years). Three did not specify age[174,180,183]. Eleven studies had neurological conditions as an inclusion criterion[154,155,158,164,169,170,179,195,196,205,208]. Seven studies did not provide any inclusion criteria[152,162,181,182,185,204,215].

2.14.3 Interventions/comparators

Eight non-pharmacological interventions for OH were identified under two general categories: *physical modalities* (exercise, electrical stimulation, compression, compression and physical counter-manoeuvres, physical counter-manoeuvres, sleeping with head up) and *dietary measures* (food and fluid intake) which aim to treat OH by raising standing blood pressure without raising supine blood pressure to increase the time people can stand, and improve their ability to perform activities of daily living.

Physical modalities

Exercise

Exercise included aerobic training using a cycle ergometer, resistance/strength training using resistance bands or weights, passive stepping using robotic tilt tables, and upper limb exercises. Seven studies included in this systematic review evaluated the effects of exercise on OH. Participants included in these studies had spinal cord injury[181], brain injury[158,205,210], brain haemorrhage[210], stroke[210], neuro cardiogenic syncope[162], Parkinson's disease[208], and OH[166,206,213].

Three studies[158,181,205] used tilt tables, two of which[158,205] used robotic tilt tables, where participants with brain injury undertook passive stepping whilst being tilted up to 65[158] and 70[205] degrees. Duration of intervention periods were different; two sessions of sequential testing[158] (intended duration of testing in minutes not reported), and 24 sessions, each 30 minutes, three times per

week[205]. The third study[181] used a tilt table and included participants with spinal cord injury who performed upper limb exercises whilst being tilted up to 70 degrees.

The effect of aerobic physical training was used in one study[162] for participants with neuro cardiogenic syncope. Participants undertook a 12-week supervised program of moderate aerobic intensity training using a cycle ergometer. Training took place twice a week and lasted for 35 minutes, and patients were instructed to perform two additional unsupervised sessions.

One study[210] examined the effect of passive stepping at 30, 50 and 70 degrees using a robotic tilt table, automated cycling in supine versus standard care (defined as mobilization with physiotherapist), for patients with severe brain injury.

Four studies[166,206,208,213] examined the effects of resistance training on elderly people with OH. In one study[206] participants performed 10 full extensions of the ankle, knee, and hip joints of both limbs starting from 60 degrees flexion of hips and 90 degrees flexion of knee and ankle joints against a resistance band (6kg load) that the participant positioned under the soles of their forefeet and firmly held at both ends whilst supine in bed prior to standing up. Participants in the three remaining studies[166,208,213] undertook a home-based resistance program, which incorporated exercises for both upper and lower limbs. These three studies were included in a meta-analysis.

Six studies[162,181,205,206,208,210] in the exercise category had a control group, which consisted of tilting only[181,205,206], standard care[208,210], and stretching and light walking[162]. In one study, participants acted as their own controls[158], and two

studies included in the meta-analysis (Section 2.14.5 Outcomes) did not include a control group[166,213].

Electrical stimulation

Electrical stimulation is a technique that uses low energy electrical pulses to artificially generate a muscle contraction of paralyzed muscles. When used in a functional context to elicit patterns of movement it is also referred to as functional electrical stimulation. The studies included in this review used electrical stimulation of upper limbs, lower limbs and abdomen.

Seven studies[152,169,170,173,179,196,215] examined the effects of electrical stimulation on OH. Participants in one study[179] had a stroke, the other six studies included people with spinal cord injury. Two studies[152,170] included the same sample and examined the same experimental interventions, differing slightly in the measured outcomes. They compared upright stationary standing versus upright dynamic standing using functional electrical stimulation, both using standing apparatus for 30 minutes on the same day. Another repeated measures study[169] positioned participants in multiple tilt angles (0, 15, 30, 45 and 60 degrees), four minutes at each angle followed by four minutes recovery, repeated with and without electrical stimulation to lower limb (bilateral knee extensors and ankle plantar flexor) muscles. One study[173] included two participants who underwent four weeks of electrical stimulation to trunk and lower-limb muscles (rectus abdominus, quadriceps, hamstrings and gastrocnemius muscles), four times per week for one hour per day. One study[215] tested the capacity of electrical stimulation, applied transcutaneously over the spinal cord (approximately corresponding to the T8 spinal segment) to manage OH in participants with spinal cord injury. Two studies[179,196] used a

robotic tilt table and electrical stimulation to compare passive stepping and passive stepping combined with electrical stimulation. These were included in a meta-analysis (Section 2.14.5 Outcomes).

Four studies included a control group[152,170,179,196], one study[173] had no control group, and participants acted as their own controls in one study.[169]

Compression

Compression involves using various types of bandages and garments on different body parts, commonly the lower limbs and abdomen. Thirteen studies[154,155,157,160,164,171,172,174,182,185,195,204,207] examined the effect of compression on OH. Participants in these studies were elderly with OH[157,160,171,172,174], had acute stroke[164], Parkinson's disease[154], neurogenic OH[155,207], or spinal cord injury[185,195,204].

Two studies[160,164], both RCTs, examined the effect of compression to both the abdomen and lower limbs. In one study[160] elderly participants with OH wore ankle to thigh bandages for 10 minutes, then an abdominal bandage was added for a further 10 minutes. Participants then wore leggings from the mid foot to the abdomen for one month at home. Authors report these were worn daily but did not report any recommendations or report usage from follow-up data. In the other study[164] participants with acute stroke wore a pneumatic abdominal binder (PAB) and pneumatic calf compression (PCC) for six consecutive sessions for approximately 15 minutes during progressive incline on a tilt table.

Three studies[154,155,195] examined the effect of abdominal compression on OH. Participants with Parkinson's disease[154] were enrolled into a randomised crossover trial. They wore an abdominal binder or placebo binder. Participants

then wore an abdominal binder every day (time not specified) for four weeks. The second study[155], a randomised crossover trial, assessed the effects of a conventional or patient-controlled adjustable abdominal binder on OH. Binders were worn for approximately 10 minutes during the testing period. The third study[195], enrolled participants with spinal cord injury into a randomised crossover trial. Participants wore an abdominal binder (pressure not reported) daily (time not specified) for six months.

Three studies examined the effect of lower limb compression during tilt tabling[174,204,207], all of which used different compression garments, different pressures, on different body parts. In one study[207] participants with neurogenic OH underwent tilt testing without and with compression applied to calves, thighs and abdomen using an inflatable G-suit to evaluate the impact of compression of different body parts on orthostatic BP and tolerance. Another study[204], a case report, tested one spinal cord injured participant on a tilt table without and then with inflatable external leg compression to bilateral lower limbs. The last study[174] tested elastic compression hosiery (tights covering the legs and abdomen) fitted to bilateral lower limbs in elderly participants.

One study[185] examined the effects of a wheelchair ergometer with and without graduated compression stockings. Spinal cord injured participants used the wheelchair ergometer twice; once with garment compression stockings and once without a week later. Further details presented in Appendix 4 (Characteristics of included studies).

One study[182] examined the effects of compression leggings at normal body temperature and a long-sleeved and legged, two-pieced, tube-lined perfusion suit at elevated body temperature in healthy older and younger adults.

Three studies[157,171,172] examined the effect of lower limb compression bandages from ankle to thigh on OH. All three studies included elderly participants who were hospitalized due to acute medical conditions[157], decompensated heart failure[171] and OH.[172] In all three studies, compression bandages were applied along both legs from ankle to thigh before sitting without compression and repeated with compression. In one study[157], compression was approximately 30mmHg compression at the ankle. The remaining two studies used 40mmHg compression[171] and 30-40mmHg compression[172] at the ankle. Both latter two studies have been included in a meta-analysis (Section 2.14.5 Outcomes).

In 10 studies participants acted as their own controls [154,155,157,160,171,172,174,182,185,203], two studies had a control group[164,207], and one study had no control group.[204]

Physical counter-manoeuvres

Physical counter-manoeuvres are specific movements or exercises such as squatting, leg crossing, tensing specific muscles with the aim of increasing standing BP and reducing OH. Four studies[165,211,212,214] were identified in the literature search which examined the effect of physical counter-manoeuvres on OH, varying in the number and type of manoeuvres performed. Participants in these studies had OH[211,212,214], neurogenic OH[165] and familial dyautomonia[193].

One study[165] examined the use of multiple physical counter-manoeuvres for 3-4 months following a training period. Training consisted of four training sessions in the laboratory performing the physical counter-manoeuvres. Participants were then asked to perform the three selected manoeuvres at home for 3-4 months when symptomatic.

In one study[211] all participants performed leg-crossing and squatting in a fixed order. Participants stood for 10 minutes maximum or until symptoms occurred, then performed leg-crossing in standing for 30 seconds then resumed normal standing. When BP dropped again, participants squatted for 30 seconds then resumed the normal standing position.

In one study[212], participants performed nine different manoeuvres, each for one minute serially, separated by 30-60 seconds of standing. Participants were asked to sit on seats of varying heights (48cm, 38cm, 20cm), with or without leg-crossing, squatting and standing in a crossed-leg position with or without additional contraction of the lower limb muscles. All manoeuvres were repeated twice and performed in a random order.

One randomised crossover trial[214] compared leg muscle pumping or tensing for one minute, commencing after two minutes of active standing, compared to active standing only.

Three studies did not include a control group[165,193,212] and two studies included a control group[211,214].

Physical counter-manoeuvres and compression

Two studies used a combination of physical counter-manoeuvres and compression. One study[203] examined the effects of abdominal compression and physical manoeuvres in participants with neurogenic hypotension. Participants maintained a standing position with the abdominal binder, and then performed physical manoeuvres in standing whilst wearing an anti-gravity suit. For nine participants the duration of standing was extended (duration not specified) by standing without crossed legs or abdominal compression. As soon as a stable

low BP was obtained for 30 seconds, the counter-manoeuvres were repeated for 90 seconds, followed by a short period of normal standing. Nine participants (unclear if it was the same nine who undertook extended standing) performed two active standing manoeuvres; external abdominal compression applied by elastic binder.

One study[193] compared the effect of physical counter-manoeuvres, one of which was abdominal compression. Participants performed four counter-manoeuvres in a randomised order and abdominal compression using an inflatable belt.

Sleeping head up tilt

One study[209] examined the effect of sleeping with the head of the bed elevated by six inches for six weeks. The control group received no intervention. One study[191] examined the effect of sleeping with the head of bed elevated with and without pharmacological intervention and 2,000ml water per day. There was no control group, but there was a control period during the first week.

Dietary measures

Food intake

Studies in this category examined the size and frequency of meals and their effect on OH. Three studies[180,183,184] examined the effect of food intake on OH.

One study[180] tested participants with Parkinson's disease and 10 age-matched controls over two consecutive days to examine the change in sBP induced by meals. They also compared the impact of orthostatic sBP response in participants with Parkinson's disease with that of control participants.

One study[183] examined the effect of meal size and the time of day on OH in elderly and young healthy participants.

The final study[184] examined the effect of meal size and number of meals in people with autonomic failure. All participants underwent the same conditions: the first day participants ate three meals, versus the second day (at least one day apart) when participants ate six meals. Total calorie intake was the same over both days.

Participants acted as their own controls in two studies[180,184] and one study did not include a control group[183].

Fluid intake

Ingesting water to increase BP and attenuate OH was examined in three studies[178,188,197]. Participants in all three studies drank 480ml fluid, however, additional variables such as food intake and exercise were also studied.
One study[178] examined the effect of ingesting water before exercise on OH. All participants had severe pre-exercise OH and underwent the same testing using a cycle ergometer. Testing was undertaken on two separate occasions; one in which participants drank 480ml distilled water.

One study[188] examined the effect of water ingestion and food intake. All participants underwent two protocols. Protocol one: participants drank 480mL of tap water; Protocol 2 participants drank 480mL of tap water immediately before eating the test meal.

The final study[197] in the category examined the effects of drinking 480ml distilled water. All participants had autonomic failure and underwent the same testing: standing BP was measured before, and 15 and 35 minutes after ingesting of 480ml distilled water.

Two studies[178,188] did not include a control group and in one study participants acted as their own controls[197].

2.14.4 Follow-up and measurement intervals

Follow-up periods varied: thirty days[179], one month[160], four weeks[154,173], eight weeks[166,205,213], twelve weeks[162,208], three to four months[165] and fourteen months.[191] Due to the wide heterogeneity in outcomes of interest, follow-up and measurement intervals are described for BP and HR only. In all other studies there was no follow-up.

Exercise

Four studies[158,181,205,206] measured outcomes of interest over one day, but all measured outcomes in various positions and at various time points. One study[181] measured from 0 to 70 degrees verticalization in 10 degree intervals, every 30 seconds at 1.5, 2.5, three, four and five-minute intervals. One study[158] measured in supine and at 30, 50 and 70 degrees verticalization every five minutes. One study[205] measured in 0, 30 and 65 degrees of verticalization for the first four minutes of every position. The fourth study[206] measured in supine, immediately upon standing, and at one, three and five minutes into standing.

In four studies, the outcomes of interest were measured pre- and post-training with follow-up at eight weeks[166,213] and 12 weeks.[162,208] One study undertook measurements in supine and at 70 degrees of verticalization.[162] The remaining three studies[213, 166,208] undertook measurements in supine, when seated and one and two minutes into standing.

Electrical stimulation

Three studies[152,170,215] tested participants on two separate days at least 24 hours apart. Two measured in supine, sitting and standing, but one[152] measured at five and 30 minutes in standing and the other[170] measured at five, 10, 20 and 30 minutes in standing. The third study[215] measured for 15 minutes in supine and sitting. Two studies[169,196] undertook measurements throughout one day. Measurements were taken at 0, 15, 30, 45 and 60 degrees verticalization at one-minute intervals[169], and every minute in supine to 80 degrees verticalization. One study[173] measured pre- and post- four weeks of electrical stimulation, every minute at 0 to 65 degrees verticalization. The final study[179] measured every minute for 10 minutes in supine to 70 degrees before and after a 30-day training period.

Compression

Nine studies[155,160,171,172,174,182,203,204,207] measured participants at one single visit. Three studies[154,157,185] measured participants over two separate days, one study[164] measured participants over six consecutive days, and one study measured participants on four separate occasions over six months.[195] Each study measured outcomes of interest at multiple time-points and in multiple positions: one[155,157,164,171,172,174], two[174], three[154,157,164,171,172,174], five[154,155,157,164,171,172], 10[154] minutes and the first and last 15 seconds of compression and deflation[203]; sitting[157,171,172,185,195], standing[154,155,182,203], supine[154,160,164,174,182,195,203,207], and at 30[164], 40[203], 45[164], 60[154,160,164], 80[207] and 90[174] degrees tilt.

Physical counter-manoeuvres

Four studies[193,211,212,214] measured participants at one single visit. Three of these measured participants in supine and standing but measured two[214],

four[193] and eighteen[212] different time-points. One study measured standing six times.[211] The final study[165] measured participants in supine, 80 degrees verticalization and standing; measures were performed 10 times over four sessions, but it was unclear whether each session was on a separate day and how many days apart. Follow-up was performed 3-4 months after session four.

Sleeping with head up

One study[191] in this category measured participants in supine and standing at four different intervals including at 14-month follow-up. The second study[209] were followed-up at the end of the six-week intervention.

Dietary measures

Food intake

All three studies measured outcomes in multiple positions at multiple time points. One study[183] measured participants over two days with an overnight stay at 12 different intervals in supine (three times) and once after one minute of standing. One study[180] measured over two consecutive days, 21 times over 10 hours in supine, sitting and standing, plus four times in supine, standing and 70 degrees verticalization. The final study[184] in this category measured participants for two days at least one day apart. Automatic ambulatory BP was measured 60 times (every 30 minutes from 0630 to 2100 hours on both days). In addition, participants initiated BP readings 11 times in lying, sitting and standing (pre-breakfast and 30 minutes following three meals; pre-breakfast and 30 minutes following six meals).

Fluid intake

Two studies[178,197] measured participants during a single visit, and one study[188] measured them on separate days (unclear if consecutive or separated). All

studies measured participants in various positions at different time intervals. One study[188] measured participants in seated (13 times protocol one and 24 times protocol two) and standing (twice protocol one) positions. One study[197] measured outcomes of interest a total of 26 times; 20 times seated and six times in standing (three times at three and five minutes of standing). The final study[178] measured participants 16 times; four times in supine and four times in standing (two and five minutes), repeated twice.

2.14.5 Outcomes

A wide variety of outcome measures were used in the included studies. The most common objective outcomes were sBP and/or dBP[152,154,155,157,158,160,164-166,169,171-174,178-185,188,191,193,195-197,203-215], HR[152,155,157,158,160,162,164-166,169-173,178-185,188,191,193,195-197,203-210,212-215], cardiac output[152,170,178,185,193,197,203,209,212,214], and stroke volume.[152,170,178,179,182,185,193,196,197,203,204,209,212,214,215] Other objective outcomes included: total peripheral resistance[152,170,178,182,193,197,203,209,212], mean arterial pressure[152,170,173,182,193,195,209,215], mean BP[154,165,191,193,196,210-212,214], oxygen saturations[157,172,204], respiratory rate[210], resistance index[165,179], HR variability[185], stroke index[165], cardiac index[165,204,207], maximum power output[185], maximum systolic velocity[179], minimum diastolic velocity[179], end diastolic index[165], peripheral resistance index[207], end diastolic volume index[207], pulsatility index[179], systemic vascular resistence[214], inferior caval vein diameter[203], femoral vein diameter[203], rate pressure product[170], perfusion index[204], cerebral blood flow[179,210], blood velocity of middle and posterior cerebral artery[215], cerebral vascular resistence[182], calf impedence[193], electrocardiographic RR-intervals[193,208], Valsalva manouvers[188,208], hyperventilation test[188], cold pressor test[178,188], oxygen uptake[185], end-tidal partial pressure of carbon dioxide[182], peak expiratory flow[195], forced expiratory flow[195], forced vital capacity[195], voice

measures[195], interruption of verticalization[158], maximal cardiopulmonary exercise test[162], fluid balance[191,209], oesophageal temperature[182], venous blood and plasma samples,[210], oedema[209].

Orthostatic symptoms were measured using a variety of methods. The most common method was self-report[157,169,171-173,178,184,191,196,197,204,209,211,212] where participants described their symptoms. One study[215] asked participants to rank their symptoms from one to 10. Other studies used formal outcome measures: Specific Symptom Scale Questionnaire for Orthostatic Intolerance[160], Global Symptomatic Improvement Score[165], Orthostatic Symptom Scale[155], Severity of OH Symptoms[207], Orthostatic tolerance[191], Symptom Change Scale[155], Orthostatic Hypotension Questionnaire[154], OH Daily Activity Scale[154], and OH Symptom Assessment[154].

Other studies included measures of muscle strength[178,179,188,208,213], one repetition maximum[166,208] and electromyography (EMG) of leg muscles[196]. Two studies measured maximum standing time[178,191]. Three studies used measures of disability and function: Timed Up and Go[213], Barthel Index[179] and modified Rankin Scale[164].

Physical modalities

Exercise interventions delivered during tilt tabling demonstrated mixed results. Greater tolerance of verticality and reduced occurrence of OH was observed in three studies[158,181,205]. Passive stepping using robotic tilt tables was effective at reducing the number of OH symptoms[158,205] and this was also observed when performing upper limb exercises during verticalization[181]. A twelve-week aerobic training programme[162] resulted in an increase in orthostatic tolerance and reduction of positive head up tilt tests. Lower limb resistance exercises[206] were

the least effective, resulting in minimal reduction in an initial fall in sBP when moving from supine to standing. No significant absolute or relative difference was observed in any of the BP components with passive cycling or passive stepping[210]. However, there was a higher difference in arterial BP in both the intervention groups compared with standard physiotherapy. Three studies[213, 166,208] investigating the effects of resistance exercise training were included in a meta-analysis (Figure 2.2), which concluded that resistance exercise training was favourable compared to no intervention, however the 95% confidence intervals for the standardized mean difference crossed zero and were wide.

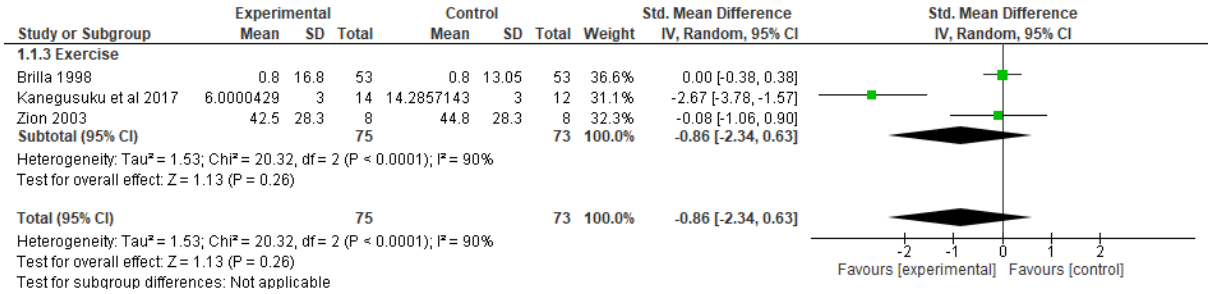
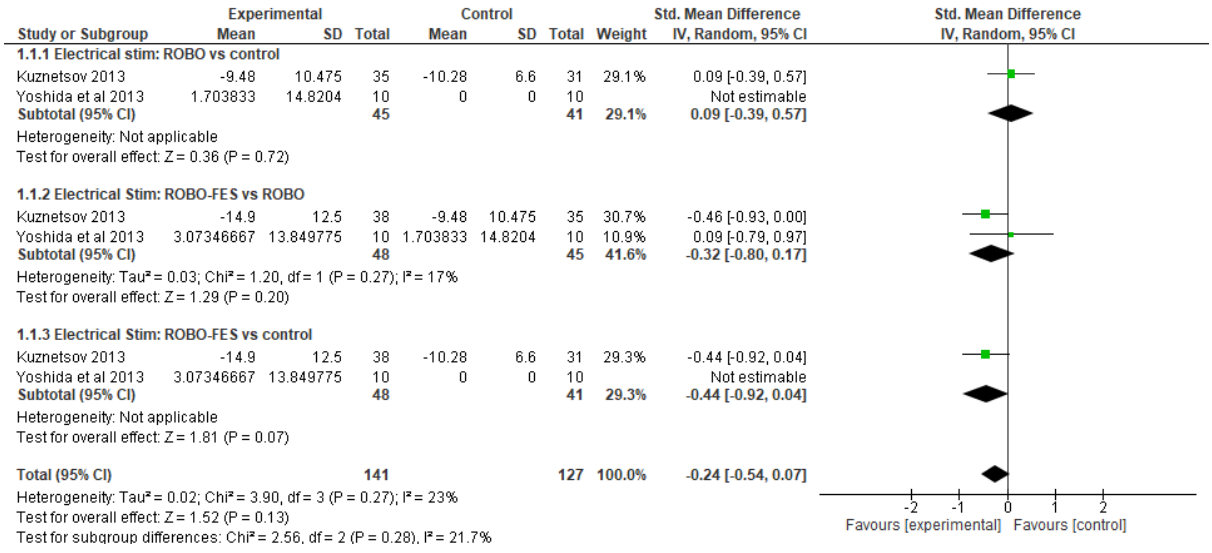


Figure 2.2 Resistance exercise compared with no intervention

Conclusion of effectiveness of exercise interventions: exercise interventions may improve orthostatic tolerance, but there were no statistically significant results with any of the exercise interventions.

Electrical stimulation was favourable in the five studies not included in the meta-analysis, wherein participants using electrical stimulation could stand for longer and had reductions in OH[152,170], demonstrated a longer tolerance time during head-up tilt[173], and normalized BP[169,215]. Passive stepping on a robotic tilt table and functional electrical stimulation was the most favourable intervention. The overall outcome of the two studies[196, 179] included in the meta-analysis

(Figure 2.3) was that electrical stimulation was favourable in treating OH, however the 95% confidence intervals for the standardized mean difference crossed zero.



ROBO: Passive stepping on robotic tilt table; ROBO-FES: passive stepping on robotic tilt table and functional electrical stimulation of lower limb muscles; Control: no intervention (Yoshida et al[196]) or tilt tabling only (Kuznetsov[179])

Figure 2.3 Electrical stimulation compared with no intervention, robotic stepping, and electrical stimulation combined with robotic stepping compared with no intervention

Conclusion of effectiveness of electrical stimulation: electrical stimulation for the studies not included in the meta-analysis was favourable, but not statistically significant. The meta-analysis concluded that electrical stimulation was favourable when comparing electrical stimulation with passive stepping, tilt tabling only, or no intervention. However, the 95% confidence interval crossed zero in two out of three of the training conditions.

Compression demonstrated positive results for elderly people with OH and people with neurogenic OH. Two studies[160,164] concluded that combined lower limb and abdominal compression improved orthostatic stability in older people and people with stroke.

Abdominal compression[154,155] was shown to reduce OH in older adults with neurogenic OH. Abdominal compression significantly reduced BP fall upon tilting[154], compared to placebo. Symptoms of OH decreased significantly at the four-week follow-up. Abdominal compression was effective at attenuating OH compared with no abdominal compression[155], and symptoms were not affected by type of binder. There was no statistically significant difference with or without abdominal binder[195], however, mean arterial BP was higher with the abdominal binder at six weeks and six months.

All three lower limb compression studies reported positive results. Maximum improvement was observed with all three combinations of compression (calves, thighs and abdomen)[207], and abdominal compression alone significantly reduced OH ($p<0.005$). Similarly, a significant improvement was observed in elderly people with OH wearing elastic hosiery tights[174], with reduction of OH at one minute ($p<0.01$) and two minutes ($p<0.005$). The spinal cord injury case report[204] demonstrated that the individual was able to remain in the upright position for longer, allowing improved mobilization during physiotherapy whilst wearing the inflatable external leg compression. The inflatable external leg compression succeeded in improving pre-syncope symptoms and preventing OH for several hours.

Participants with spinal cord injury demonstrated an increase in sympathetic activity and a decrease in parasympathetic activity after maximal exercise whilst wearing graduated compression stockings using the wheelchair cycle ergometer[185].

Lower limb compression stockings[182] caused a passive physical resistance that, upon standing, delayed the maximal drop in mean arterial pressure in both

younger and older adults. The authors of the study concluded that compression stockings appeared to reduce venous pooling, however, the total peripheral resistance increased in older participants in minute six. There were no differences between groups when heat and orthostatic stress were combined.

Lower limb compression bandages[157] decreased OH symptoms in participants who were medically unwell including 14 with stroke. Approximately 55% of participants experienced symptoms in the un-bandaged group. Significant changes were observed in the un-bandaged group compared to the bandaged group with significantly greater incidence of palpitations, tachycardia and decline of oxygen saturation over time ($p < 0.04$, <0.03, <0.03 respectively). Authors did not report results for sBP or dBP. Results from the two studies[171, 172] included in the meta-analysis favour compression bandaging (Figure 2.4), however the 95% confidence intervals for the standardized mean difference crossed zero.

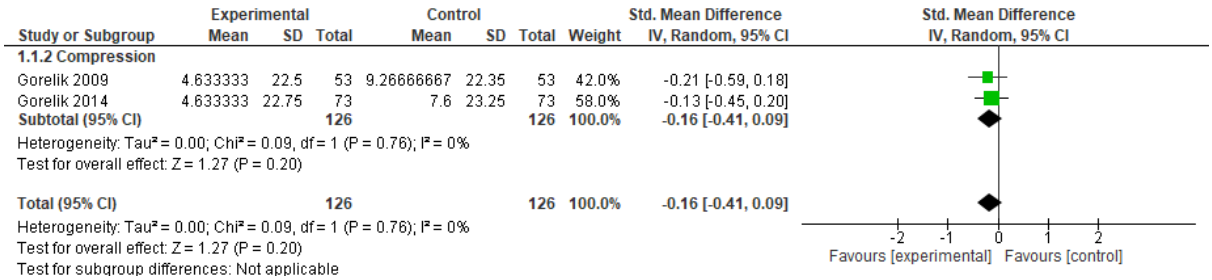


Figure 2.4 Compression bandaging compared with no intervention

Conclusion of the effectiveness of compression interventions: lower limb and abdominal compression[160,164,207], lower limb compression[157,171,172,174,182,185,204] and abdominal compression[154,155,207] are effective in improving OH. However, not all studies were statistically significant, hence, the benefit of undertaking a meta-analysis.

Physical countermanouvers[165] were deemed effective in reducing OH in people with neurogenic OH, if performed correctly. Squatting produced the most dramatic change in arterial BP, resulting in longer standing time improved. The follow-up survey identified that the use of the manoeuvres varied from once to 11 times per day (3.83(±3.1) manoeuvres per day). However, the follow-up survey was conducted via telephone, therefore it was unknown whether participants were performing manoeuvres correctly.

Leg crossing and squatting[211] improved standing BP in people with autonomic failure. After leg crossing, all participants stood for 10 minutes or more (pre-intervention standing times not provided). Time in standing after squatting was not reported.

Leg crossing and leg muscle contractions[212] resulted in higher standing BP than without leg muscle contraction. Leg crossing whilst sitting on 48cm and 38cm chairs demonstrated an increase in sitting BP in people with pure autonomic failure.

Leg muscle pumping (tiptoeing and leg crossing)[214] had different effects on OH in people with autonomic failure. Tiptoeing did not change BP after one minute in the patient group, but the normative group showed an increase in BP. Leg-crossing increased BP in both groups initially, which was more pronounced in the normative group.

Physical manouvres[193] that significantly increased mean BP included bending forward ($p<0.005$), squatting ($p<0.002$) and abdominal compression ($p<0.04$) but not leg crossing. Squatting and abdominal compression also induced a significant increase in cardiac output during squatting ($p<0.02$) and during abdominal compression ($p<0.014$).

Conclusion of effectiveness of physical countermanouvers[165,193,211], leg crossing[211,212,214], leg muscle pumping/contractions[212] and bending forward[193] improved OH, whilst tiptoeing did not[214].

A combination of abdominal compression and physical counter-manouvres[203] had a significant effect on standing BP ($p<0.05$). However, there were no significant differences in the effect of abdominal compression on the diameter of caval or femoral veins, or compression and arterial pressure response.

Conclusion of the effectiveness of a combination of abdominal compression and physical counter-manoeuvres: A combination of abdominal compression and physical counter-manoeuvres is effective in treating OH.

Sleeping with head up[191] reduced the drop in BP after one minute of standing ($p<0.01$ for sBP). Four of the six participants received sleeping with head up alone, and five participants received combined treatment (sleeping with head up and pharmacological treatment using Fludrocortisone). Combined treatment was most effective, significantly reducing OH symptoms in all patients ($p< 0.001$), increasing the maximal standing period to at least 10 minutes compared to 35 to 170 seconds pre-treatment. Sleeping with head-up at six inches for six weeks[209] had no effect on OH symptoms and BP.

Conclusion of the effectiveness of sleeping with head: Sleeping with head up in combination with Fludrocortisone is more effective than sleeping with head up alone.

Dietary measures

Food intake had a negative effect on BP in elderly people and people with neurogenic OH. Participants with Parkinson's disease had a significant ($p<0.01$)

postprandial sBP drop in supine position compared to healthy controls[180]. There was a greater fall of sBP with passive versus active standing in both groups, with a greater postprandial fall in the group with Parkinson's disease. The authors reviewed one meal (lunch) and did not look at all meals throughout a whole day, nor collect data on the size of meals participants usually ate with those provided in the study.

Post-meal BP was lower in all positions[184] (lying sBP $p<0.005$, lying dBP $p<0.02$; sitting dBP $p<0.07$; standing dBP $p<0.06$) after three large meals. Compared to six meals, sBP and dBP between meals reached lower levels on the three-meal study day. Fewer symptoms were reported during the six-meal study day.

Post-meal supine BP was significantly lower ($p<0.02$) in older participants[183]. Supine sBP and dBP was significantly higher ($p<0.15$ and $p<0.001$) in the elderly group but standing sBP and dBP was similar between groups.

Conclusion of effectiveness of food intake interventions: Eating smaller, more frequent meals as opposed to larger, less frequent meals resulted in significantly higher supine, sitting and standing BP and improved OH symptoms in people with autonomic failure, neurogenic OH, elderly people and people with Parkinson's disease'.

Fluid intake prior to standing had a positive effect on OH in various positions. Five minutes after drinking water, there was a significant rise in BP in the supine position ($p<0.05$)[178]. With exercise there was a clear fall in BP, this occurred even after water ingestion. Blood pressure remained low after exercise but was significantly higher ($p<0.05$) after water intake, resulting in better tolerance of post-exercise standing. Water drinking improved orthostatic tolerance post-

exercise. Standing prior to water ingestion caused a significant fall ($p<0.01$) in BP in all participants[188]. After water ingestion there was a rise in seated BP. Seated and standing BP at 15 and 35 minutes after water ingestion was significantly higher ($p<0.01$, $p<0.001$) than before water, with an improvement in orthostatic symptoms.

Drinking 480mls of water at room temperature in less than five minutes improved standing BP and orthostatic tolerance in people with autonomic failure[197]. The response was similar in patients with multiple system atrophy and those with pure autonomic failure. Water ingested before a meal attenuated postprandial hypotension in these patients. Drinking water also attenuated orthostatic tachycardia in people with idiopathic orthostatic intolerance.

Conclusion of effectiveness of fluid intake interventions: Ingestion of water increases BP in supine[178], sitting[188] and standing[188,197]. Water ingested prior to a meal also attenuates postprandial hypotension[197].

2.15 Discussion

This review set out to examine the effectiveness of non-pharmacological interventions to treat OH in elderly people and people with a neurological condition.

Whilst the literature contained many non-pharmacological interventions to treat OH in these populations, the review highlighted a heterogeneity of methods. The inclusion criteria included some participants who did not have a formal diagnosis of OH prior to entering a study. Many studies included participants with neurological conditions such as Parkinson's disease, brain injury, stroke and spinal cord injury, but did not specify OH as an inclusion criterion. This may be because OH in neurological conditions is associated with central autonomic

dysfunction and/or the absence of vein blood pump related to lower limb paralysis. Further, periods of immobility or prolonged bed rest, which can cause physiological changes such as diminished sympathetic activity[216], in combination with hypovolemia, may also predispose some individuals with neurological conditions to OH. However, authors did not explicitly provide this as a rationale for their chosen sample.

Thirty-one percent of studies specified OH in their inclusion criteria, but there was heterogeneity in the definitions used, and only 26% provided a definition, which makes meaningful comparison difficult. The most commonly used definition was a sustained drop in sBP of at least 20 mmHg and/or dBP of at least 10 mmHg following a change of posture, which was applied to various postures (standing, tilting (ranging from 15-90 degrees tilt angles) or sitting). Other variations used a higher threshold[155,193,207]. Using higher thresholds could result in participants being missed during screening. It also raises the question as to whether the lack of standardization observed in these studies, is mirrored in clinical practice. The time points at which BP was measured also varied from immediately[160,206] to up to 10 minutes[166,179] of being upright. Further, the definition of “being upright” varied from 60-90 degrees on a tilt table or self-initiated standing, and authors did not acknowledge or discuss the differences of active and passive standing. Verticalization using a tilt table does not fully replicate the physiology of active standing because the exercise reflex and the mechanical squeeze on the venous capacitance and arterial resistance vessels are less[217]. Therefore, OH may occur more frequently with tilt table testing[218].

Cerebral hypoperfusion is acknowledged in clinical guidelines[105,136] as a very common cause of syncope or transient loss of consciousness[219], which is likely

to impact on standing time and symptoms experienced. Monitoring cerebral blood flow is important in people with acute or sub-acute stroke, because autoregulation is impaired following stroke[130]. Two recent meta-analyses[220,221], for example, concluded that OH was independently associated with a significantly higher risk of developing coronary heart disease, cardiovascular disease and heart failure. Despite the relative importance of maintaining cerebral blood flow when standing upright, it was measured in only two studies. One study[210] monitored cerebral blood flow, but only in participants with sub-arachnoid haemorrhage and not in participants with ischemic stroke or severe brain trauma. The authors acknowledged the potential risk of impairing cerebral blood flow during mobilization but did not provide a rationale for only monitoring participants with sub-arachnoid haemorrhage. Additionally, they did not provide any data on cerebral blood flow. The second study[179] included 104 participants with stroke, all of whom had cerebral blood flow measured pre- and post-training. Cerebral blood flow was reduced ≤10%, but participants were asymptomatic. Asymptomatic OH is more common than symptomatic OH[222], which means clinicians may be unaware of the potential risk of further brain damage when these patients are being mobilised and/or undergoing therapy. As well as measuring cerebral blood flow, future work should also investigate what is a clinically important drop in cerebral blood flow.

2.15.1 What type of interventions worked?

Overall, the results were mixed. Although effect sizes often favoured the intervention in individual studies, meta-analysis of three interventions were non-significant, as highlighted in the forest plots in Figures 2.2, 2.3 and 2.4. Of the additional interventions reviewed, physical counter-manoeuvres and fluid intake produced favourable results. It is important to consider the feasibility and

practicality of these interventions if they are to be implemented into clinical practice.

Physical counter-manoeuvres were favourable in reducing OH, for example, but people with balance and mobility problems may find many of the physical manoeuvres challenging, and their risk of falling increased. Additionally, performing these physical manoeuvres requires the ability to stand and move between sitting and standing, and people with moderate and severe disability would often not be able to perform these movements without mechanical/physical assistance. Exercise was favourable, but the changes measured were not statistically significant. The resistance training programs may also be unsuitable for people with moderate to severe disability. Several studies used robotic tilt tables and automated cycle ergometers to passively move lower limbs during verticalization, which may be more suitable for people with neurological conditions who have moderate to severe disability. When considering implementation into practice it is important to consider how accessible this equipment is; robotic tilt tables, for instance, are not routinely available in clinical practice.

Other interventions that may be suitable for people with moderate to severe disability are compression and electrical stimulation. Compression garments, such as compression stockings, may allow repeated safe standing and/or sitting out. They can be used in conjunction with tilt tabling and standing frames to facilitate orthostatic tolerance, and are frequently used in spinal cord rehabilitation[223]. In stroke, current clinical guidelines recommend intermittent pneumatic compression or graded compression stockings of lower limbs as thromboembolism prophylaxis[224]. Therefore, abdominal binders may be more

appropriate as they would not interfere with this. Furthermore, abdominal binders may be easier for healthcare providers to monitor skin integrity, and provide less risk of skin damage, although they would be contraindicated for people receiving nutritional support via a gastrostomy tube, because the binder would compress the gastrostomy tube and may cause pain and skin damage. Additionally, people with moderate to severe disability may need assistance to don and doff compression garments.

Electrical stimulation is an adjunctive intervention commonly used in clinical practice to treat muscle impairment[225]. Contraindications for electrical stimulation include poor skin integrity, significant autonomic dysreflexia in incomplete spinal cord injury above T6, and uncontrolled epilepsy[226]. Only one study[173] provided this information. None of the studies discussed the implications of contraindications of using electrical stimulation in clinical practice. However, contractions induced by electrical stimulation of lower limb muscles may activate the skeletal muscle pump as effectively as voluntary contractions of these muscles in people without weakness or disability as a result of stroke or neurological impairment. This may allow patients to stand earlier or for longer during rehabilitation sessions or performing activities of daily living.

Water ingestion had a positive effect on OH and would be suitable for many people. However, stroke and degenerative neurological conditions can cause swallow impairments[227], therefore, ingesting water quickly may be unsafe and/or challenging for these people due to risk of aspiration and aspiration pneumonia. Further, people who have incontinence, and/or reduced mobility that affects their ability to get to the toilet, may be reluctant to undertake this

intervention. This intervention would also be unsuitable for people who have fluid restriction due to other medical conditions. All three studies tested water ingestion on a one-off basis, thus, the accumulative effects are unknown.

Long-term follow-up and prolonged intervention regimes were lacking in most studies. Therefore, it is unknown whether OH improves over time with repeated application of a specific non-pharmacological intervention, and whether any improvements are sustained, thereby alleviating the need for further intervention over the longer term. None of the studies evaluated the instantaneous versus training effects (e.g. repeated interventions) of the different OH interventions. For example, an abdominal binder improved OH when it was worn for four weeks[154], but there was no follow-up beyond this point, so it was not known if symptoms returned once it was no longer worn. This warrants different trial designs with longer follow-up periods.

Determining long-term effect is important because studies suggest the cardiovascular system can adapt over time to develop orthostatic tolerance. In spinal cord injury, for example, these adaptations may be due to changes in Rennin–angiotensin–aldosterone activity[228,229]. Further, adaptations in the central control of autonomic functions have been identified in healthy animals with prolonged exercise training and may occur over time and with training in people with OH[230].

There may be a difference in the short and long-term effects of the interventions between conditions. Where there is direct damage to autonomic centres such as seen in multiple system atrophy[231] and Parkinson's disease[232], the potential for adaptive changes may be limited. In contrast, there may be greater potential for central and neuro-hormonal adaptive changes in the elderly and after stroke,

where causes may be more linked to paralysis and long-term immobility. This highlights the need for future studies to stratify participants according to both their condition and stage or severity of disease. Different conditions have different pathophysiological mechanisms underlying OH[233-235], and thus potentially different short and long-term effects of an intervention.

2.15.2 Implications for practice

The findings of this systematic review have several implications for clinicians working with people with neurological conditions and elderly people in both inpatient and community settings. The meta-analysis concluded that electrical stimulation, lower limb compression and resistance exercise training were favourable in reducing or abolishing OH, although the GRADE certainty of evidence was very low for all three physical modalities. These modalities could be implemented into rehabilitation sessions for people with stroke, neurological conditions and elderly people.

Many rehabilitation units have cycle ergometers (e.g. MotoMED or TheraTrainer) which patients could use whilst sitting out, even in specialist wheelchairs. However, depending on the severity of disability some patients may need supervision to optimize safety. Additionally, many rehabilitation units also have access to functional electrical stimulation (e.g. MicroStim) which could be incorporated into standing practice to increase the duration of standing and optimise physical activity during rehabilitation sessions. However, clinicians need to check whether patients have any contraindications, for example, people with spinal cord injury above T6, uncontrolled epilepsy, poor skin integrity or cognitive problems.

When OH is problematic, lower limb compression and abdominal binders could be used, both within and outside of rehabilitation sessions, to optimise physical activity. Abdominal binders are easier to don and doff than lower limb compression stockings and this may enable patients to carry this out independently. For those who require assistance, education of clinicians, carers and family members would be required to enable this to be undertaken both within and outside of rehabilitation sessions, and in the community setting.

The applicability of water ingestion for people with neurological conditions has been acknowledged in the discussion. However, if patients have been screened by Speech and Language Therapists and deemed to have no swallow impairment, sipping water may be a useful way of managing OH during standing practice.

This review suggests a range of non-pharmacological interventions may be effective in managing OH. Most do not require specialist equipment and training therefore the cost of implementation is likely to be minimal. Importantly, from a practical perspective, it is apparent that many of these interventions can be incorporated into and/or outside of rehabilitation sessions. However, patient's physical abilities and impairments should be considered when selecting which non-pharmacological interventions to implement e.g. cognitive impairment, severity of disability, swallow impairment and other medical conditions.

2.15.3 Conclusion

The review found mixed results for the effectiveness of non-pharmacological interventions to treat OH in people aged 50 years and over and people with a neurological condition. Setting, participants, outcomes, study designs and intervention types were heterogeneous, resulting in an inability to include all

studies into a meta-analysis. There are several non-pharmacological interventions effective in treating OH (electrical stimulation, lower limb and abdominal compression, physical manoeuvres, resistance exercise training, eating smaller more frequent meals and drinking 480ml water), but not all have resulted in clinically meaningful changes in outcome. Some may not be suitable for people with moderate to severe disability, for example, they may be unable to stand to perform physical manoeuvres or perform resistance training due to weakness. Thus, it is important for clinicians to consider the patient's abilities and impairments when clinically reasoning which non-pharmacological interventions to implement. Participants in this feasibility trial have severe stroke and will be unable to perform physical manoeuvres, or resistance exercises. They may have impaired swallow and likely wear pneumatic compression stockings therefore abdominal binders will be used in the OH protocol.

2.15.4 Limitations

The primary limitation of this review is the heterogeneity of methods of the studies included. Most studies had small sample sizes which limits generalizability of the results. The methodological quality of the included studies varied. For RCTs randomization not used or unclear, blinding in most RCTs was low. Some quasi-experimental studies did not include a comparator or control group. The number of participants in each experimental group varied in the different studies included in the meta-analyses varied. The certainty of the evidence was very low for all studies included in the meta-analysis, thus any translation into practice must be tentative. Subgroup analysis was not possible due to insufficient studies included in the meta-analysis, as well as inconsistency of reported demographics, medications, and severity of neurological condition using disease specific validated outcome measures. The

meta-analysis supports the adoption of abdominal binders in the OH protocol used in the feasibility RCT. This aligns with recommendations that non-pharmacological treatments for OH should be considered first before progressing to pharmacological treatments[23,136].

This review was further limited by the inclusion of only English language studies.

2.15.5 Recommendations for future research

This systematic review highlighted heterogeneity in measurement of non-pharmacological interventions to treat OH. Lack of a standardized approach to measurement in OH trials makes consolidation of the body of knowledge difficult, which may negatively impact on effective interventions being implemented into clinical practice. A consensus is required when measuring BP at specific time-points during standing or verticalization. Further, a consensus is required for measuring OH in people with neurological conditions who have impaired mobility and reduced standing times. Additionally, a core set of outcome measures and standardized time points would facilitate pooling of results in meta-analyses, to enable more accurate conclusions to drawn.

Standardization of inclusion criteria is required to ensure all participants enrolled in OH intervention studies have OH, either by testing during screening or from a formal diagnosis. Improved consistency of reporting of methodology, as recommended by the Consolidated Standards of Reporting Trials guidelines[236] is also recommended. Consistency of reporting demographics, medications, and severity of neurological condition using disease specific validated outcome measures would allow sub-group analysis.

2.16 Summary

Chapter 2 has presented the results of the systematic review, which suggest several non-pharmacological interventions are effective in treating OH in people with a neurological condition. However, due to time constraints, the review was completed after recruited closed. Thus, the OH protocol used in the feasibility RCT only included abdominal binders, which were deemed favourable in treating OH. The OH protocol will need to be developed further prior to progressing to a definitive trial.

Chapter 3 presents the feasibility trial methodology.

Chapter 3 Feasibility trial methodology

3.1 Research problem and uncertainties

Standing up early after stroke has the potential to prevent or minimise secondary complications in the musculoskeletal and cardiorespiratory systems which can be detrimental to recovery of independence in ADL. Performing functional tasks such as standing and sit to stand early after stroke may result in adaptive neuroplasticity and improve functional outcome. Standing and sit to stand are functionally linked tasks but this novel combination has not been tested in people with severe stroke, therefore its efficacy in this patient population is unknown. Due to the profound disability caused by a severe stroke, individuals require physical and mechanical assistance to perform these activities. A standing frame would enable people with severe stroke to practise prolonged standing and task-specific training (repeated sit to stand); combining these two interventions will create a functional standing frame programme. The functional standing frame programme will address a key priority for people who have suffered a severe stroke who have identified that standing up soon after their stroke was an “important milestone” in their recovery. However, several uncertainties exist which need to be understood prior to progressing to a full-scale trial.

3.2 Uncertainties to be addressed

It is not known if it is feasible to undertake a RCT of a functional standing frame programme for people with severe stroke. Therefore, prior to progressing to a main trial, a feasibility trial is indicated to inform the design the main trial[238]. This chapter presents the research methodology and rationale for the feasibility trial.

3.3 Trial aims, objectives and research question

3.3.1 Trial aims

The **primary aim** was to establish whether a RCT of a functional standing frame programme (intervention) versus usual physiotherapy (control) in people with severe stroke in an inpatient sub-acute stroke rehabilitation setting is feasible.

The **secondary aim** was to explore experience of the intervention and associated procedures from the perspective of participants, their relatives and physiotherapists delivering the trial, using qualitative methods.

3.3.2 Trial objectives

Feasibility trial objectives were set according to the following indicators to assess :

Process

Eligibility criteria, ability to consent, consent rate, recruitment rate, willingness/ability of physiotherapists to recruit, willingness of participants to be randomised, retention rate, acceptability of the intervention, determining usual physiotherapy, sample size estimates, primary outcome, end point.

Resource

Burden (participants and treating research physiotherapists/assessors).

Management

Participant adherence, acceptability of outcome measures to participants and physiotherapists, fidelity, OH protocol.

Safety

Safety was assessed by comparing the number and nature of serious adverse events (SAEs) and adverse events (AEs) in both the intervention and control group.

Further details on these indicators are contained in the Statistical Analysis Plan (Appendix 5).

Objectives related to the qualitative component were to explore:

- How trial procedures (timing and mode of participant recruitment, information provision, methods of data collection for example timing and content of outcome measures) can be refined to maximise recruitment, retention and acceptability in the definitive trial
- Participants' experience of the intervention
- Participants' experience of being randomised
- Participants' reasons for, and experience of, withdrawing from the trial
- Relatives' influence of participants' decision to consent to participate, remain in the trial or provide assent for their relative
- Physiotherapists' attitudes, thoughts and feelings of implementing the intervention and whether they perceive a subsequent RCT to be achievable
- Physiotherapists' attitudes, thoughts and feelings of the trial documentation and trial procedures.

3.3.3 Research question

Does early standing and sit to stand practice, using a standing frame in people with severe sub-acute stroke lead to an improvement in functional ability and quality of life and a reduction in neuromuscular impairment?

However, this question will not be answered in this feasibility trial. The aim is to determine if this trial is feasible prior to progressing to a main trial to test effectiveness.

3.4 Trial design and justification

A pragmatic, multi-centre, parallel single-blinded two-armed feasibility RCT was deemed appropriate to determine the feasibility of a functional standing frame programme for people with severe stroke versus usual physiotherapy during their inpatient sub-acute rehabilitation. A feasibility RCT with a nested qualitative component (semi-structured face-to-face interviews and focus group) was chosen to determine, in the first instance, whether the implementation of a definitive RCT would be feasible in the future.

A cluster RCT was initially considered, where each SRU would be randomised as opposed to individual participants[239]. However, this would have prevented the intervention and associated trial procedures to be tested and evaluated across all four SRUs. Additionally, usual physiotherapy practices would have been limited to only two SRUs, which would have limited the ability to describe physiotherapists' current clinical practices for people with severe stroke during sub-acute inpatient rehabilitation. The RCT was chosen as the most appropriate method to answer the research question in a future definitive trial, as it is considered the 'gold standard' due to its rigorous and robust method of determining whether a cause-effect relationship exists between the intervention

and outcome[240,241]. The RCT is a fundamental part of clinical research, and highly regarded because it has the potential to reduce bias related to confounding variables through a control group and selection bias through randomisation[242]. In this feasibility RCT participants were randomly allocated to one of two groups: the functional standing frame group (intervention) or the control group (usual physiotherapy).

Qualitative research was embedded in this feasibility trial to provide insights into the intervention and trial procedures. The use of qualitative research within feasibility RCTs is becoming increasingly common[243]. It has been identified as useful to examine and address key uncertainties concerning intervention content and delivery (acceptability, feasibility and fidelity etc.); trial design, conduct and processes (impact of trial on participants and staff, recruitment and retention, acceptability of the trial in principle and practice etc.); outcome measures (breadth, selection, accuracy and completion)[243]. This is discussed further in Section 3.19.

The intervention combined two physiotherapy interventions that have been separately evaluated and reported in the literature; prolonged standing and task-specific strength training. Currently, it is not known whether this novel combination of physiotherapy for people with severe stroke is effective.

The functional standing frame programme is a complex intervention and the United Kingdom Medical Research Council (MRC)[244] provides guidance on developing and evaluating complex interventions. A key component of the evaluation is the acceptability among people engaged in the feasibility trial, e.g. people with severe stroke, their relatives, treating physiotherapists and research assessors. Acceptability has been defined as “a multi-faceted construct that

reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate, based on anticipated or experiential and emotional responses to the intervention"[245]. Currently it is unknown whether the intervention would be acceptable to, or tolerated by, people with severe stroke, at this early stage of their rehabilitation continuum. Thus, this feasibility trial was used to determine whether the intervention was appropriate for further testing; enabling assessment of whether a main trial is feasible[246].

This feasibility RCT was a multi-centred using three healthcare sites (four SRUs) based in two counties in the South West Peninsula, England. The rationale for a multi-centre trial was to include a broader range of SRUs that may improve subsequent generalisation of findings, as well as increase the number of clinical judgements concerning the acceptability and feasibility of the intervention. It reduces the possibility of local phenomenon for trial processes and procedures and is more reflective of a subsequent national main trial. This design provides the opportunity to determine and describe what usual physiotherapy practices are in sub-acute inpatient stroke rehabilitation for people with severe stroke that has been identified as an important factor in the success of stroke rehabilitation trials[247]. Furthermore, there is access to a larger number of potential participants as well as ability to compare results among SRUs.

Details of what treatments physiotherapists are implementing as usual physiotherapy during rehabilitation sessions with people with severe stroke were gathered using a Physiotherapy Content Recording Tool (Appendix 6: Treating Therapist Control Group CRF). This will enable current practices to be described and highlight whether current practices align with current evidence-based recommendations. National clinical guidelines[3] recommend physical

rehabilitation post-stroke should focus on mobility, balance and walking to facilitate independence in ADL. Evidence for task-specific strength training and early mobilisation is provided in these guidelines, however, it is not known if or how physiotherapists are routinely implementing these evidence-based interventions with people with severe stroke. Various approaches to physical rehabilitation are used after stroke[248], yet there is no standard treatment protocol which enables physiotherapists to implement multiple approaches. Additionally, there is potential for physiotherapists to follow a single approach to the exclusion of others, and for their practice to be based on personal preference as opposed to scientific rationale[248].

Risk of contamination was identified as a potential problem in the current feasibility RCT where individuals allocated to the control group may inadvertently receive some aspects of the standing frame intervention as physiotherapists at each of the sites were treating participants in both groups. The trial protocol explicitly states that treating physiotherapists should not alter their usual physiotherapy practice during the trial, and this was emphasised in face-to-face training. However, it was acknowledged that physiotherapists may perceive the intervention to be effective and this could 'unconsciously' influence their usual physiotherapy practice over time[249]. Treating physiotherapists documented the content of their usual physiotherapy sessions. This enabled treatment activities implemented to participants in this group to be reviewed to determine any deviations from the protocol during the recruitment period. Additionally, fidelity checking was conducted to establish physiotherapists' adherence to the trial protocol and whether the intervention and control was delivered as specified in the protocol[250]. See Process Evaluation (Section 3.13).

The current feasibility RCT design reduces bias. Recruitment bias was eliminated as physiotherapists were unaware of group allocation until informed consent/assent was received and baseline blinded assessments were undertaken by an independent blinded assessor. Additionally, the current RCT design ensured the assessor was blinded to group allocation.

Blinding is a key methodological procedure in RCTs[251]. The ideal is for both participants and assessors to be blinded to treatment allocation[252]. However, for pragmatic RCTs in areas such as physiotherapy rehabilitation, double-blind trials are often impossible to achieve[253,254]. Thus, blinded outcome assessment was used in this feasibility RCT to limit bias[254]. Blinded outcome assessment refers to the process of concealing treatment group identity from outcome assessors, after their treatment assignment through randomisation, to minimise the occurrence of biased assessments influencing research findings[255].

All blinded assessments were undertaken in separate visits independently of delivery of the trial intervention or usual care sessions. The baseline assessment was undertaken by a blinded assessor, after written informed consent was obtained by the research physiotherapist, prior to randomisation. Every effort was made throughout the trial to ensure assessments were blinded. Treating physiotherapists and/or participants were reminded not to discuss their allocated group with the assessor during any interaction. The success of blinding in this trial was formally tested by asking blinded assessors to guess group allocation during each assessment visit and comparing these responses to what would be expected by chance[256,257].

3.5 Participants

In keeping with the pragmatic trial design, eligibility criteria were kept broad.

Inclusion criteria were:

1. A confirmed clinical diagnosis of new (first/recurrent) severe stroke, cerebral haemorrhage or infarct confirmed by consultant or CT scan leading to admission to the SRU
2. Aged ≥18 years
3. Graded as mRS 4 or 5 and/or National Institutes of Health Stroke Scale (NIHSS)[258] ≥16 (severe or very severe stroke and unable to stand without support/mechanical aid and assistance of two people)
4. Able to give informed consent, or assent received from a consultee (see recruitment section)
5. Conscious and responsive to verbal commands.

Exclusion Criteria were:

1. Systolic blood pressure ≤100mmHg or ≥220mmHg at rest, lying or sitting
2. Oxygen saturation ≤87% with or without supplementary oxygen (e.g. severe acute/chronic cardiorespiratory disease)
3. Resting heart rate of ≤40 or ≥110 beats per minute (e.g. cardiovascular instability)
4. Temperature ≥38.5 degrees centigrade or ≤35 degrees centigrade
5. Orthopaedic impairments which prevent full weight bearing in standing
6. Malnutrition Universal Screening Tool score of ≥2, or deemed to be not meeting nutritional demands for therapeutic

interventions by dietician

7. Documented clinical decision for receiving end of life care
8. Unstable coronary or other medical condition that is judged by the Principal/Chief Investigator (PI/CI) or clinical team to impose a medical risk to the patient by involvement in the trial
9. Assessed functionally by specialist physiotherapists as being a risk to themselves or others due to their inability to follow non-verbal prompts or are behaving erratically
10. Immobile and not weight bearing pre-stroke
11. Additional neurological deficits unrelated to the current or past stroke (e.g. peripheral neuropathy or Multiple Sclerosis, because these impairments are not related to the condition of interest)
12. Weight of 115kg or more (weight limit on the standing frames)
13. Being discharged out of county, e.g. admitted during holiday/visit to Cornwall or Devon because they would be unable to participate in follow-up assessments
14. If people are registered in another trial the CI was contacted to ensure there was no conflict between trials
15. Non-English speaking.

Eligibility criteria for clinical trials can affect recruitment and retention[259]. To optimise potentially beneficial treatments being used in clinical practice, it is important to ensure eligibility criteria is representative of the overall population to whom the intervention is intended for[260]. Eligibility criteria for this trial were selected using literature from relevant research trials and discussions with specialist physiotherapists in inpatient sub-acute stroke rehabilitation. This was

to ensure the participants included in the trial were representative of the patient population physiotherapists routinely see in their clinical practice in SRUs. Stroke is predominantly, although not exclusively, prevalent in older people[261] who are highly likely to have co-morbidities in conjunction with their stroke[262]. To facilitate a representative sample, comorbidities were not excluded.

People with cognitive and communication impairments are frequently excluded from clinical trials[248,263]. Exclusion of such impairments may be due to interventions requiring a specific level of ability, or challenges around informed consent. Given that 75% of people post-stroke experience significant cognitive impairment[264] and over a third of people experience speech and language impairments (aphasia) post-stroke[265] arguably these people should be included in an evaluation of the functional standing programme as they constitute those to whom these trial results would be especially applicable. Thus, people with cognitive and communication impairments were not excluded.

3.6 Recruitment

Identification and recruitment of potential participants was conducted on admission to participating inpatient SRUs by physiotherapists. This was supported by the local National Institute for Health Research (NIHR) Clinical Research Network (CRN). Physiotherapists logged all admissions and screened patients for stroke severity. All patients classified as a severe stroke (mRS 4 or 5) were screened for eligibility (see Appendix 7: Screening CRF and Appendix 8: Post-Screening CRF) and eligible participants were approached within 48 hours of them being deemed medically fit for rehabilitation, or as soon as practicable. Potential participants were given a Participant Information Sheet (PIS) (Appendices 9-11 Participant Information Sheets). There were three

different versions of the PIS to accommodate different levels of communication and cognition.

3.7 Randomisation

Eligible consented participants were randomly allocated to either the intervention or control group using a secure centralised web-based system. Randomisation took place after the baseline assessment. Randomised allocations were computer-generated by the Peninsula Clinical Trials Unit (PenCTU) in conjunction with an independent statistician, in accordance with the PenCTU's standard operating procedure. The randomisation list and the program were stored in a secure network location within the PenCTU, accessible only to those responsible for provision of the randomisation system. This ensured concealment of allocation for the physiotherapists undertaking recruitment and the blinded assessors.

A minimisation procedure (which has a random element) during the randomisation process was used to reduce possible imbalance between the two groups. Minimisation factors were:

1. Fatigue at baseline assessment, scored by the participant and measured using a Visual Analogue Scale (VAS) (fatigue (VAS: 4-10) vs. no/minimal fatigue (VAS: 0-3))
2. Presence of OH at baseline, tested using manual sphygmomanometer and a standardised protocol (a decrease in systolic blood pressure of 20mmHg or more, or a reduction in diastolic blood pressure of 10mmHg or more, upon changing body position from supine to an upright posture in sitting or standing)[126].

After randomisation, an automatic email was sent by the PenCTU to the relevant treating physiotherapist to notify them of each participant's allocated group. Notification of randomisation (but no details regarding group allocation) was emailed to the CI/blinded assessor.

3.8 Intervention group

The intervention was protocolised to be delivered once a day over three weeks. It aimed to start as early as possible after randomisation to ensure treatment was completed during participants' inpatient admission. A detailed description of the intervention can be found in the Work Instruction (Appendix 12). The Work Instruction required physiotherapists to check participants' BP for the first three sessions, or until BP was within the participants' normal range on three consecutive sessions. If a participant had a drop in sBP of at least 20mmHg and/or dBP of at least 10mmHg within three minutes of moving from supine or sitting into standing, physiotherapists were directed to the OH protocol (Appendix 13).

The programme consisted of 5-7 sessions per week for three weeks. Each session was protocolised to last for 45 minutes: 30 minutes (or as long as tolerated) using the standing frame which included standing and repeated sit to stand (up to 8-12 repetitions). Eight to 12 repetitions was based on exercise recommendations for people with stroke[266] and discussions with physiotherapists and occupational therapists working with people with severe stroke during the design of the trial. There was an additional 15 minutes (or as long as tolerated) to provide time for usual physiotherapy where participants could practise transfers, upper limb activities or activities chosen by participants

or guided by physiotherapists. The target number and duration of sessions is aligned with current RCP Guidelines[3].

The initial frequency and duration of standing was anticipated to vary according to physical capability as assessed by the treating physiotherapist. The aim was to progress standing time and sit to stand repetitions by 30% in each session up to the maximum of 30 minutes and 8-12 repetitions per session. Each treating physiotherapist used their individual clinical reasoning when evaluating participants' tolerance to standing and ability to tolerate incremental increases in standing duration.

Should participants improve to the extent where support from the standing frame was not required, participants could progress to unsupported standing outside of the frame or walking to optimise physical recovery for the remainder of the 3-week intervention. However, the protocol stipulated participants needed to continue with sit to stand repetitions within each 30-minute session.

Physiotherapists were required to record activities undertaken during every session using a Physiotherapy Content Recording Tool (Appendix 14: Treating Therapist Intervention CRF). This standardised checklist is based on the Stroke Physical Therapy Intervention Tool[267], which provides a system for recording physiotherapy treatment for stroke patients. This Recording Tool was modified to reflect current clinical practice in a sub-acute rehabilitation setting. Recording physiotherapy interventions during sub-acute stroke rehabilitation enabled usual physiotherapy management to be described.

For the first three sessions (or longer if deemed appropriate by therapists), blood pressure was assessed both prior to and during standing. This was based

on the protocol used in the feasibility and safety testing of a very early rehabilitation trial[82].

3.8.1 Standardisation of the intervention

Use of standing frames is incorporated within undergraduate physiotherapy training in the UK and is a recognised core skill for neurological physiotherapists. To standardise and optimise implementation of the intervention, treating physiotherapists received face-to-face training and an information pack.

Treating physiotherapists were required to record any deviations from the protocol on a Protocol Deviation form.

3.9 Control group

This was defined as usual physiotherapy delivered during stroke rehabilitation for 45 minutes once a day (or as long as a tolerated) for a target of 5-7 sessions per week which aligned with RCP Guidelines[3]. Physiotherapists recorded activities undertaken during every session using the Physiotherapy Content Recording Tool contained in the Control Group CRF (Appendix 6).

3.10 Assessment

Participants were assessed at baseline (prior to randomisation), three weeks (at the end of the intervention period) and 3, 6 and 12 months (Appendix 15: Assessor CRF). Assessments aimed to be completed within ±seven days of the assessment due date provided by the PenCTU's centralised website.

3.11 Outcome measures

Standardised, validated clinician-rated and patient self-reported clinical outcomes were measured in both groups. There is no core set of standardised

outcome measures for stroke and no agreed upon time-points when outcomes should be measured. Physiologically, the biggest changes post-stroke occur within the first three months as discussed in Chapter 1, Section 1.3, and the Stroke Recovery and Rehabilitation Roundtable taskforce[11] have developed a framework defining critical time-points post-stroke that link to the currently known biology of recovery: baseline, post-intervention, 3-6 and >6 months. They do not explicitly suggest 12-month follow-up; however, a scoping review suggests that improvements in participation occur up to 12 months post-stroke[268]. Thus, outcomes in this feasibility trial were measured at baseline, post-intervention, 3-, 6- and 12-months post-intervention. All the outcome measures listed below were undertaken at each of the follow-up trial visits.

3.11.1 Proposed primary outcome measures for the anticipated main trial

To facilitate comparison between the intervention and control groups in the anticipated main trial, an outcome measure relevant to the clinical question and valid for the population studied was required[269]. The proposed primary outcome measure assessed functional ability in performing ADL. Functional ability was identified as being important and a priority for people with severe stroke and their relatives during discussions in the development of this trial. People associated functional status with being independent in undertaking ADL which was a priority and meaningful for them.

The Barthel Index of Activities of Daily Living (BI)[270] is frequently used in stroke clinical trials, although was not designed specifically for this purpose. The BI rates a person's degree of independence performing functional self-care (feeding, grooming, bathing etc.) and mobility activities (transferring in/out of bed/chair, walking etc.). Advantages of the BI are its simplicity and ease of administration and its convenience and low cost in longitudinal assessment[271].

A major limitation of the BI is its floor effect[272] with its limited ability to detect change at extremes of ability, making it less discriminating in severe stroke[273].

This feasibility trial provided the opportunity to investigate whether an alternative functional outcome measure is more responsive to detecting change in people with severe stroke and can be used in both inpatient and community settings for both the acute and chronic stages of stroke. Therefore, the Edmans Activities of Daily Living Index for Stroke Patients[274] (Edmans) was also used. This measure covers all the categories included in the BI; however, the degree of independence is more detailed than dependent/independent for each item assessed. It was developed specifically for people with stroke, both as an inpatient in the sub-acute phase as well as in the community setting in the chronic phase. Collecting both these outcomes enabled investigation of the clinical utility and responsiveness of two functional outcome measures, to determine which measure will be used in the anticipated main trial.

Both the BI (self-report version) and the Edmans are self-report. However, given the prevalence of communication and cognitive impairments, participants may be unable to report this information or may have reduced insight into their actual versus perceived abilities. In cases where it was not possible to obtain all the outcome measurement data from the participant, the researcher obtained proxy data from the treating physiotherapist during inpatient admission or next of kin/carer once discharged from hospital.

3.11.2 Proposed secondary outcome measures for the anticipated main trial

Proposed secondary outcome measures are listed in Table 3.1

Outcome measure	Measurement domain	Description
Hand held dynamometer[275,276]	Knee muscle strength	Knee extensor strength is strongly correlated to common daily functional activities such as the ability to sit to stand, stand and walk in people with sub-acute stroke[275,276]. Quadriceps strength on both lower limbs was explored using a portable hand held dynamometer. This involved measuring the maximal isometric strength with participants in standardised position of side lying with knee at 90-degree flexion. It is reliable in measuring lower limb strength in people with stroke (ICC=0.88-0.98)[277].
Manual universal goniometer[278]	Length of hip flexors, hamstrings and ankle plantarflexors	Hip flexors, hamstrings and ankle plantarflexors are all muscles that cross two joints and hence are at higher risk of contracture (especially within the first six weeks post-stroke[279]) which can directly impact negatively on function and societal participation. Goniometry is the most commonly used instrument by physiotherapists in both clinical and research practice and is a simple and quick method of assessing the degree of contracture at any joint[280]. Passive range of movement of these muscles was measured on both lower limbs. Intra-rater reliability using goniometry to measure ankle plantarflexor length is moderate to good (ICC: 0.719-0.892) and inter-rater reliability is moderate (ICC: 0.725-0.741) in people with stroke.
Modified Ashworth Scale[281]	Muscle tone in hip adductors, hamstrings and ankle	Increased muscle tone was measured in the hip adductors, hamstrings and ankle plantarflexors. Spasticity is common post-stroke and may interfere with functional activities and cause pain and further complications such as loss of range of joint movement[282]. The Modified Ashworth scale was used. This rates tone on a 4-point ordinal scale (0=no increase in muscle resistance, 4=affected part(s) rigid in flexion or extension). This shows: good inter-rater reliability hip and knee (weighted kappa=0.82) and ankle (weighted kappa = 0.74); moderate intra-rater hip (weighted kappa = 0.45), good intra-rater reliability for knee (weighted kappa = 0.62) and very good for the ankle plantarflexors (weighted kappa = 0.85) people with stroke[283].

Trunk Control Test[284,285]	Control of trunk	Trunk control is strongly correlated to common daily functional activities such as the ability to sit, sit to stand and walk[286,287]. The Trunk Control Test measures four simple aspects of trunk movement. The patient lies supine on the bed and is asked to roll to the weak side, roll to the strong side, sit up from lying down and sit in a balanced position on the edge of the bed, with feet off the ground for a minimum of 30 seconds. Movements are rated using a 3-point ordinal scale (0= unable to do without assistance; 12= able to do so using non-muscular help or in abnormal style; uses arms to steady self when sitting; 25= able to complete task normally)[285,286]. These are very low-level activities that reflect the abilities of people with severe stroke in the acute/sub-acute phase of stroke[285], although it is acknowledged that this measure of low-level activity has the potential for a ceiling effect for people who improve at various stages of their rehabilitation continuum. An alternative is the Trunk Impairment Scale which is reported to have no ceiling effect[286]. The Trunk Impairment Scale evaluates static and dynamic sitting balance as well as co-ordination of trunk movement. However, this measure would be too challenging and subsequently has a floor effect with people with severe impairments post-stroke[288].
Patient Health Questionnaire (PHQ-9)[289] or Stroke Aphasia Depression Questionnaire-10 (SADQ-10) for participants who have aphasia[290]	Mood	Psychological mood disturbance is associated with higher rates of mortality, long term disability, hospital readmission, suicide and higher utilisation of outpatient services if untreated[291-293]. The National Institute for Health and Clinical Excellence (NICE)[294] and RCP Guidelines[3] recommend routine assessment and management of mood after stroke. Mood was assessed using the Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 is a 9-item summed scale with scores ranging from 0 (no depressive symptoms) to 27 (all symptoms occurring daily). It shows good sensitivity (78%) and specificity (96%) for any depression diagnosis regardless of age, gender or ethnicity[289]. It was administered by the assessor and reported by the participant. Some participants with significant aphasia required assessment with the Stroke Aphasia Depression Questionnaire-10 (SADQ-10). This is scored out of 30 with ≥14 = depression. This is an observer rating of observed behaviour on a 4-point scale and has good internal consistency (Cronbach's alpha =0.80

		and a split-half reliability of r =0.81)[290]. The SADQ-10 hospital version was used whilst an inpatient and the SADQ-10 community version was used once discharged from hospital. The clinical care team completed the SADQ-10 during inpatient stay and relatives or caregivers were asked to complete in the participants' place of residence. The blinded assessor then reviewed this as it is an observational measure over the proceeding seven days.
Stroke and Aphasia Quality of Life Scale-39[295] and the EQ-5D 5L[296]	Health related quality of life	Health related quality of life (HRQoL) measures are relevant in stroke because the key aims of rehabilitation are to maximise functional independence as well as facilitate adaption to disability, promote social and community integration and maximise well-being and quality of life[295]. The Stroke and Aphasia Quality of Life Scale-39 item (SAQOL-39) is a stroke specific HRQoL instrument. The 12 domains (energy, family roles, language, mobility, mood, personality, self-care, social roles, thinking, upper extremity function, vision, work/productivity) were obtained from interviews with stroke survivors and subsequently modified by stroke and rehabilitation experts. Each domain is scored 1 = couldn't do at all, 5 = no problem with a total score out of 195 (all four subgroups combined). Lower scores = more trouble with activity. Internal reliability of the domains are high (alpha = 0.74-0.94) and test re-test reliability is also good (ICC =0.89)[295]. However, it is unknown whether it is feasible for people with severe stroke to use this outcome measure, given the high incidence of cognitive and communication impairments post stroke[264,265]. Ceiling effects have been reported in the language domains in people with nil, mild or moderate aphasia[295]. There is no evidence on the responsiveness of this measure. The feasibility of a health economic evaluation using HRQoL was evaluated by using the EQ-5D (5L)[29]. The EQ-5D (5L) is a valid and reliable simple questionnaire in health-related research and provides a simple descriptive profile and a value for health status and takes five minutes to complete.

		However, this is a generic measure and uncertainties exist regarding the appropriateness of the EQ-5D (5L) for people with severe stroke. Proxies were used if participants were unable to complete the questionnaire. Each of the five questions are scored 1 = no problem to 5 = unable. The Health State is scored out of 100. 100 = best health.
Visual Analogue Scale to enable people with aphasia to also rate their level of fatigue[297]	Fatigue	Fatigue is one of the most distressing symptoms after stroke and can adversely affect ability to carry out ADL, return to work, participation in rehabilitation programmes and quality of life[298,299]. Prevalence of post-stroke fatigue stroke spans from 29% to 77%[299], ranges from mild to severe[300] and is reported by stroke survivors to persist two years post-stroke[301]. Several assessment scales exist to measure fatigue, many of which are stroke trials[302,303]. The most commonly used is the Fatigue Severity Scale[304] which is a 9-item self-report questionnaire designed to assess fatigue over the past two weeks. The high incidence of communication and cognitive impairments suggests many participants would not be able to complete this questionnaire. However, given the significant adverse effect of fatigue it was essential to optimise inclusion of people with severe cognitive and communication impairments. Therefore, a visual analogue scale was used. This enabled people with or without aphasia to objectively score their fatigue: where 0 indicates “Not tired at all” and 10 indicates “So tired I can’t do any more” (Figure 3.1). Fatigue was categorised as mild (1-3), moderate (4-6) and severe (7-10) based on a previous study of post-stroke fatigue[304]. A highly significant correlation ($r = 0.69$, $P < 0.01$) was observed between Fatigue Severity Scale scores and fatigue as indicated on a VAS[306].

Table 3.1 Proposed secondary outcome measures for the anticipated main trial

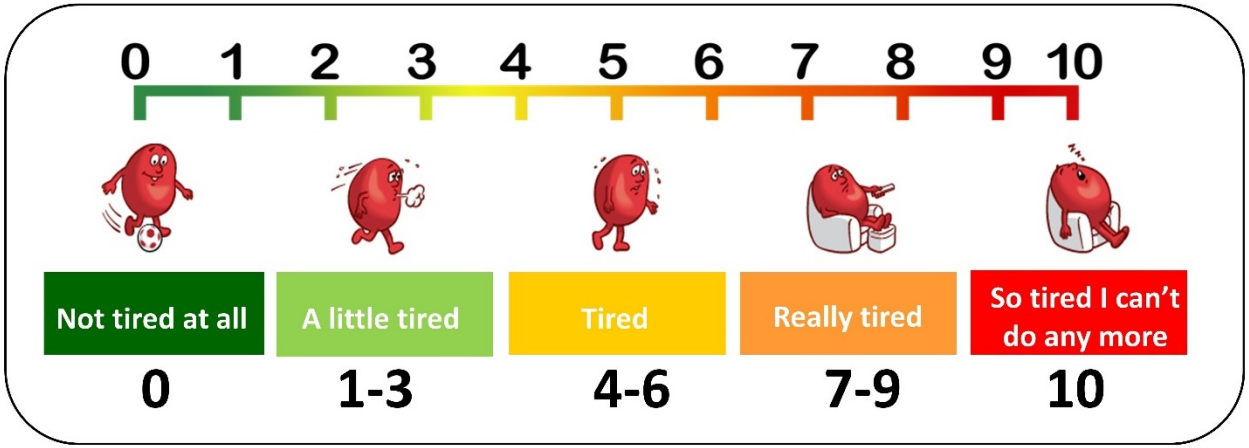


Figure 3.1 Fatigue Visual Analogue Scale

3.12 Economic evaluation

As this is a feasibility trial an economic evaluation was not carried out. However, the data set for the EQ-5D (5L) were collected to determine the feasibility of people with severe stroke being able to complete this given the high prevalence of communication and cognitive impairment.

3.13 Process Evaluation

This feasibility trial is considered as the modelling phase of the MRC guidelines for developing complex interventions[115]. As a feasibility trial, the purpose is not to make a formal analysis of the primary outcome, but to evaluate trial processes to determine whether to progress to an effectiveness trial and to estimate unknown parameters needed to design this trial.

Process evaluation is a key part of the intervention development process to enable conclusions to be made about the strengths and weaknesses of a trial. This will facilitate decision-making for the anticipated main trial. The MRC guidance[115] recommends process evaluation and highlights the importance of capturing fidelity (whether the intervention was delivered as intended); dose (the quantity of intervention implemented) and reach (whether the intended audience comes into contact with the intervention, and how).

Fidelity was measured using several mechanisms: treating therapists recorded the content of their physiotherapy sessions in the CRFs; an independent assessor observed 10% of sessions in both the functional standing frame intervention and the usual physiotherapy groups across all four healthcare sites and completed a fidelity checklist (Appendix 16), and during qualitative interviews with treating therapists.

3.14 Safety monitoring

Throughout the trial, all possible precautions were taken to ensure participant and physiotherapist safety and wellbeing. Participants in both groups were monitored for AEs via completion of the brief interview after every therapy session during the three-week intervention period.

Treating physiotherapists were asked to report AEs related to the intervention (e.g. falls, musculoskeletal aches and pains, fatigue) and all SAEs to the research team, regardless as to whether they were thought to be related to the intervention or not; and whether they believed these AEs/SAEs were related to the intervention or not. Additionally, participants were monitored during their scheduled follow-up visits for AEs and SAEs. AEs were reviewed regularly by the Trial Management Group (TMG) to determine the relatedness of these events to the intervention. SAEs were reviewed by the Trial Steering Committee (TSC).

Physiotherapists followed local policy with regards to documenting AEs and SAEs in patients' medical notes or other monitoring systems.

3.15 Retention rates and withdrawal

Each participant had the right to voluntarily withdraw from the trial at any time, without any effect on their current or future care.

Any participant could at any time after they consented decide that they no longer wished to be part of the trial. Withdrawal may have been through personal choice (i.e. they withdrew their consent), in consultation with a health professional, for example where it became impossible to provide outcome data or comply with any other trial procedures for whatever reason, or on the recommendation of a health professional following an AE or SAE. In addition,

the treating physiotherapist, doctor or other health professional responsible for the participant could have suggested withdrawal following a significant protocol deviation, such as a participant being found to be ineligible post-randomisation. Ineligible participants would have been withdrawn from the trial. Number and reasons for withdrawals were recorded and reported by the treating physiotherapist using a standardised proforma. Participants who were withdrawn (except any who were deemed ineligible post-randomisation) were asked to remain in the trial for follow-up assessments as per protocol, although it was acknowledged that if a participant was receiving end of life care this would not be appropriate.

To ensure the CI remained blinded, treating therapists could discuss any potential withdrawals with a member of the research team to ensure the treating therapists were supported in this process.

3.16 Statistical analysis

3.16.1 Sample size

As a feasibility trial, a formal sample size calculation based on considerations of power was not appropriate and hence this trial was not powered to detect between-group clinically meaningful differences in a primary outcome. One of the aims of this trial was to provide robust estimates of the likely rates of recruitment and follow-up, as well as estimates of the variability of the proposed primary and secondary outcomes to inform sample size calculations for the anticipated trial. There is no consensus on the recommended number of participants required for a feasibility trial, with published “rules of thumb” ranging from 20 to 70 or more participants, when the planned primary outcome is of a continuous nature. For example, a recent paper recommended a feasibility trial

sample size should recruit 25 participants per allocated group, if the anticipated trial has a two-arm parallel group design, with 90% power and two-sided 5% significance level, to detect a “small” standardised effect size[307]. Therefore, this feasibility trial aimed to recruit 50 participants in total.

It was anticipated that 60% of participants randomised would complete their 29- and 55-weeks post-randomisation follow-up assessment. This included an estimated 40% drop out rate due to mortality[308,309].

3.16.2 Statistical analysis plan

In keeping with the aims of a feasibility trial, a detailed statistical analysis plan was developed by the CI and approved by statisticians and the TSC, prior to the final database lock and analyses (Appendix 5 Statistical Analysis Plan).

3.17 Protocol compliance

Any protocol deviations, non-compliances, or breaches of the approved protocol were documented on the relevant form by a relevant member of the research team, or the CI or blinded assessor, and reviewed by the CI. Significant or repeat episodes of non-compliance were reported by the CI to the TMG (including the Sponsor) and every effort made to prevent further occurrences. Frequently recurring protocol deviations were not acceptable and would have required immediate action and potentially classified as a serious breach.

3.17.1 Notification of serious breaches to Good Clinical Practice and/or the protocol

A serious breach to the Good Clinical Practice (GCP) and/or the protocol was a breach that was likely to affect to a significant degree:

1. the safety or physical or mental integrity of the trial participants
2. the scientific value of the trial
3. the conditions and principles of GCP in connection with the trial

3.18 Determining progression to the full trial

This research will progress to a full trial application if minimum success criteria are achieved in key feasibility aims and objectives, and/or if solutions to overcome any issues can be identified. These criteria are listed in Table 3.2.

	Criteria	Scenario 1	Scenario 2	Scenario 3
1	% of recruitment target achieved (50 participants)	≥70% of the target figure	51-69% of the target figure	≤50% of the target figure
2	Target figure = 75% of the percentage of participants randomised to the intervention group who participated in at least five sessions per week of the intervention (e.g. 30 minutes of standing, or a 30% increase in standing time every session, and 8-12 sit to stand repetitions). This includes an estimated dropout rate of 25% due to mortality[308,309]	≥70% of the target figure	51-69% of the target figure	≤50% of the target figure
3	Target figure = 60% of the percentage of participants randomised who completed their 29- and 55-weeks post-randomisation follow-up assessment. This includes an estimated 40% drop out rate due to mortality[308,309].	≥70% of the target figure	51-69% of the target figure	≤50% of the target figure
	Proposed action	**Proceed to submitting plan to funder for full trial**	**Discuss with TSC and funder about progression and resources needed to achieve target**	**No progression to plan a full trial in the current design**

Table 3.2 Criteria for progression to a full trial

3.19 Qualitative component

Qualitative methods were used alongside quantitative methods to provide the opportunity to explore, examine and address key uncertainties prior to the anticipated main trial[243]. The combination of both qualitative and quantitative research is recommended for complex interventions to understand barriers to participation and provide insights into important processes and experiences of the intervention and trial processes[114,115]. An embedded design was considered important to facilitate meeting the aims and objectives of this feasibility trial.

Qualitative data were collected using semi-structured interviews and a focus group. This methodology is ideally suited to a feasibility trial where uncertainties exist and offers the opportunity to explore people's experience of being involved in the trial, identifying and overcoming barriers to recruitment[240]. Interviews and focus groups were conducted by the author.

A topic guide (Appendix 17), with suggested questions and prompts helped guide interviews using open-ended questions, while enabling me to respond flexibly to the flow and direction of the interviewee's responses[311]. This was developed in collaboration with people with stroke, relatives, physiotherapists and supervisory team. I used an iterative and reflexive approach to interviews, the notion that data from interviews and data analysis and reflection shaped subsequent interview topics guide.

3.20 Participants (qualitative component)

Participants were eligible for interview if they were:

1) Able to use a range of communication methods including speech, gesture and/or writing as determined by the Consent Support Tool as well as other assessments determined appropriate by the

Speech and Language Therapist based on the SRU.

2) Able to recall involvement in the trial or trial processes with or without prompts or aids (e.g. trial documentation) as required.

Eligible relatives were given a PIS (Appendix 18 Relative Participant Information Sheet). Relatives were eligible for interview if they were:

1. Aged ≥18 years
2. A family member/close friend of a participant enrolled in the trial
3. Able to provide written informed consent for a semi-structured interview related to their family member/close friend's participation in the trial.

Eligible physiotherapists were given a PIS (Appendix 19: Physiotherapist Participant Information Sheet). Physiotherapists were eligible for interview and/or focus group if they were:

1) A registered physiotherapist working on the SRU for three or more days in each week

2) Willing to provide written informed consent for a semi-structured interview and subsequent focus group at the end of the recruitment period related to the feasibility of implementing the intervention and associated trial procedures.

Exclusion criteria for participants were severely impaired communication and/or deficits in cognitive skills or hearing which impacted on their ability to participate in an interview.

3.20.1 Sampling

Stratified purposive maximum-variation sampling was used to best inform the qualitative component aims and objectives and ensure that participants selected were relevant to the topic being explored[312] and had the cognitive and/or communication ability to participate.

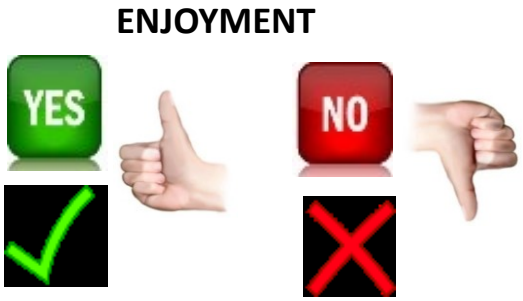
The aim was to interview up to one third of participants (n=16) which included participants who participated in the intervention group (n=6) and control group (n=6) sessions as well as those who declined to participate or withdrew (n=4). Additional interviews involved up to eight relatives and eight treating therapists (including PIs) which was proportionate to each SRU. This was to gather a broad representation of views and experiences within the time limits of this three-year fellowship[313]. However, I acknowledge that due to the severity impairments in this patient population, the prevalence of severe cognition and communication impairments may have potentially limited the number of participant interviews. I aimed to interview people with mild to moderate aphasia because it was important to seek the perspectives and experiences of people with aphasia due to its high prevalence post-stroke. A member of the research team who did not require blinding undertook the sampling in discussion with me because I was aware of participants' communication and cognitive impairment thus their ability to participate in an interview.

3.21 Data collection

A combination of data collection methods were offered for the qualitative interviews: semi-structured face-to-face, telephone or Skype based on suggestions from patient and relatives during trial design. All participants were offered a date, time and venue (when face-to-face) convenient for them.

Interviews and the focus group were digitally audio recorded, transcribed verbatim and anonymised.

Participants' may experience recall bias[314] (e.g. memory impairment post-stroke or pre-existing). To address this and maintain blinding during the three-week intervention, a brief interview was used with each participant following each intervention session. A visual analogue scale was used to allow participants to rate their fatigue, enjoyment and effort and body aches and pains (Figure 3.2), responses to which were documented in the intervention CRF.



Please mark on the body chart where the participant reports or indicates any aches or pains.

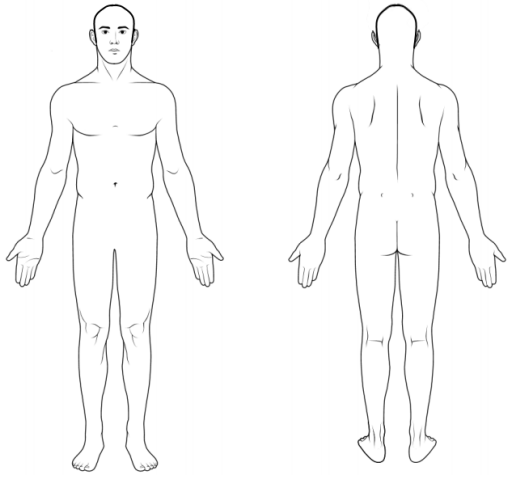
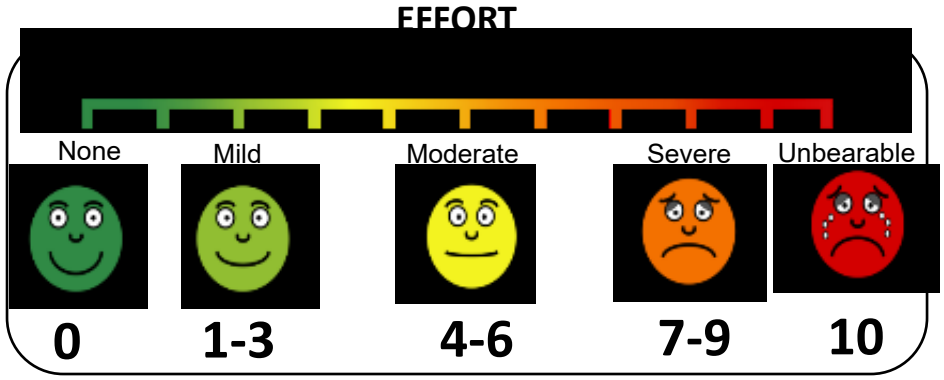
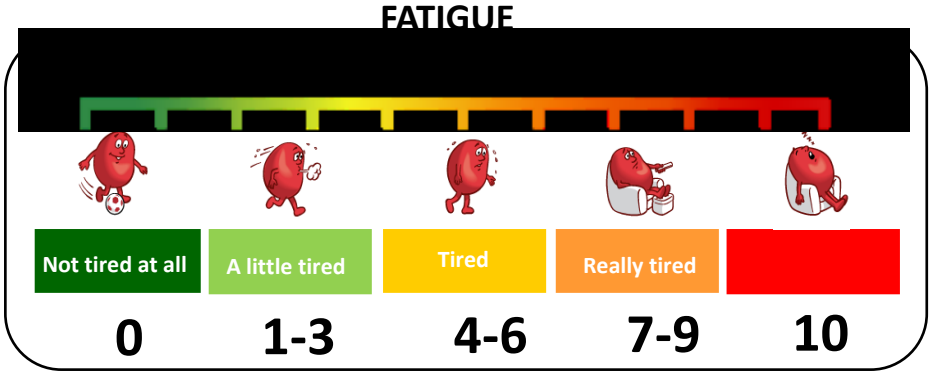
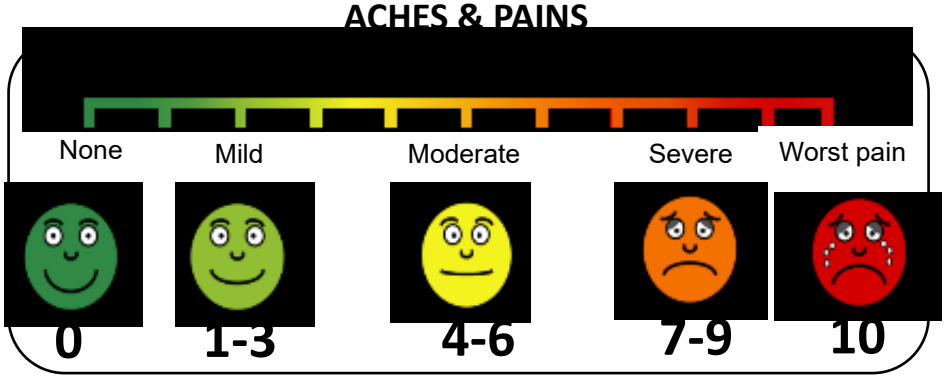


Figure 3.2 Brief interview questionnaire







Physiotherapist interviews were conducted approximately three months after recruitment commenced and at various times throughout the trial depending on opening of sites and staff availability, and a focus group approximately one month after recruitment closed.

Interviews with two people with stroke from each site who declined to participate or withdrew from the trial were planned to provide insights into trial procedures that could be addressed prior to a subsequent main trial to optimise recruitment and retention.

I transcribed all interviews and focus group recordings which were digitally recorded. Where possible, I transcribed the interviews the same day as the interview, and in advance of subsequent interviews. This enabled me to reflect and take an iterative approach to the topic guide and note where prompts or change of wording were required for future interviews.

3.21.1 Safeguarding of adults

If participants disclosed information to me or any other member of staff involved in the trial, or the staff had concerns about participants experiencing, or being at risk of abuse at any point during the trial, they were advised to follow relevant local and national safeguarding procedures.

3.22 Data analysis

All transcribed data were transferred into NVivo software[315] and all transcripts were analysed using thematic analysis[316,317].

Thematic analysis is an approach informed by Braun and Clarke[316,317] who identified six phases of analysis: a) familiarisation with the data, bi) generating initial codes, c) searching for themes, d) reviewing themes, e) defining and naming themes, and f) producing a report. Thematic analysis was chosen as

the method of analysis for several reasons. First, it can be considered a foundation method of analysis, suitable for novice qualitative researchers[317]. Second, thematic analysis is flexible, in that it is not aligned with a particular epistemological, philosophical or theoretical approach[316-318]. Finally, I wanted to perform an inductive analysis, whereby themes (patterns of meaning) are derived directly from the data, rather than from interview questions or my preconceptions[316-318].

Transcripts were coded using extracts from the data, to remain close to the data. Each unit of analysis was analysed in groups (e.g. all patient participants were analysed together).

Some transcripts were reviewed by supervisors to provide opportunity to discuss codes. Once all transcripts had been reviewed and coded in NVivo, all codes were printed out and cut into separate pieces and stuck to a wall. I had intended to use NVivo to combine codes, but I found this restrictive, and tacking codes to a wall enabled me to see all the codes and organise into groups, considering how different codes may form an overarching theme. Group codes were typed up and I used supervision sessions to identify relationships between codes, between overarching themes and subthemes to develop themes. Cross-cutting of data enabled me to review any physiotherapist-participant dyad, e.g. any differences between what physiotherapists and participants said.

Original transcripts were then reviewed to ensure the themes were an authentic representation of the data. Interview and focus group participants were invited to review an initial draft of the themes, to ensure the analysis represented an accurate overview of participants' views and experiences. Data was also

presented to physiotherapists and fellow PhD colleagues to facilitate develop of themes.

3.23 Trial management and monitoring

3.23.1 Data management

The PenCTU were responsible for data management for the trial. Data were recorded on trial specific CRFs by the treating physiotherapists and blinded assessors. Completed forms were sent to the PenCTU and entered onto a secure web-based database. All data were double entered and compared for discrepancies. Discrepant data were verified using the original paper data sheets. Data were collected and stored in accordance with the Data Protection Act 1998 and General Data Protection Regulations 2018 and are accessible for the purposes of monitoring or auditing.

3.23.2 Trial oversight

Two committees were involved in the set-up, management and oversight of this trial: the TMG and TSC. The TMG comprised individuals involved in the development of the protocol and the day-to-day running of the trial. They were responsible for all practical details of the trial, ensuring it was progressing to time, monitoring AEs and recruitment and attrition.

The TSC was responsible for overseeing the conduct of the trial on behalf of the Sponsor and funder and comprised a group of experienced trialists with majority independent representation including patients and members of the public. The TSC monitored the scientific integrity of the trial including trial progress, adherence to the protocol, reviewing accumulating safety data to monitor participant safety.

3.24 Ethical issues

Ethical approval for the trial was granted by the National Research Ethics Scheme (NRES) Committee Wales (Reference number: 16/WA/0229) and the Health Research Authority (HRA) (Reference number: 201646). The International Standard Randomised Controlled Trials Number is 15412695. Royal Cornwall Hospitals NHS Trust were the trial sponsors (Reference number: 2016.RCHT.009). The trial was funded by NIHR as part of a Clinical Doctoral Research Fellowship Award (Reference Number: ICA-CDRF- 2015-01-044).

The trial was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki principles of Good Clinical Practice[319], and the Department of Health Research Governance Framework for Health and Social Care[320].

3.24.1 Consent

In line with GCP, PIs at each site had overall responsibility for informed consent of participants at their site. PI's took responsibility for ensuring all vulnerable people were protected and participated voluntarily, free from coercion or undue influence.

To make the decision to participate in the trial, written informed consent was received if the person was deemed to have capacity or capacity was not doubted under the Mental Capacity Act 2005[321] (See Appendix 20 Patient Consent form). Participants had the right to withdraw from the trial at any time for any reason without adversely affecting their ongoing care and their decisions respected.

Aphasia, cognitive and/or visual impairments can impact on the ability to read and understand participant information sheets and provide consent. If capacity was doubted due to aphasia, Speech and Language Therapists used the Frenchay Aphasia Screening Test[322] (FAST) (recommended in the Royal College of Physicians Guidelines for Stroke[3] to confirm the presence of aphasia. They used the Consent Support Tool[323] to identify the optimum format in which to present the research information during their subsequent capacity assessment. If capacity was doubted due to cognitive and/or visual impairment the OT undertook their routine assessments and utilised this information to indicate the style of information participants were most likely to understanding during their capacity assessment to consent for trial enrolment.

Capacity assessments were carried out by one or two members of the patient's usual clinical care team (depending on local policy) and included an OT or Speech and Language Therapist to ensure their cognitive and/or communication needs were supported appropriately. The outcome of the capacity assessment was communicated to the PI or authorised delegate to enable them to undertake the consent process if the participant was deemed to have capacity.

For participants who were unable to provide written consent (e.g. unable to write due to aphasia or apraxia) but could verbally consent or point to an appropriate tick or yes diagram, a witness was permitted to sign and date on the participant's behalf. A consultee was approached when participants were deemed to lack capacity (see Section 3.24.2).

Ethical approval was granted to gain immediate consent due to the nature of the research (dealing with new disability, potential for impaired recall of details and

the need to instigate the trial in a sub-acute setting and not delay the onset of the intervention). However, potential participants and consultees had the opportunity to speak to any member of the clinical care team, research team or family about the trial and have time to consider providing consent/assent, if requested.

3.24.2 Assent by consultee

Potential participants lacking capacity were included in the trial if a consultee provided written assent (See Appendix 21 Consultee declaration form). A "personal consultee" is someone engaged in caring for the participant (not professionally or for payment) or is interested in his/her welfare and is prepared to be consulted. If a personal consultee was not identified or willing to act as consultee, the PI could consult a "nominated consultee", e.g. a person independent of the projected appointee in accordance with the Department of Health's Guidance on nominating a consultee for research involving adults who lack capacity to consent[324]. Consultees were given information about the trial and advised what the participant's wishes and feelings would be about taking part in the trial. The consultee gave advice rather than consent. The advice of the consultee was respected.

Trial documentation accessible for people with aphasia was produced using resources from the NIHR[325], in collaboration with stroke specialist Speech and Language Therapists. Appropriate time was allowed for questions/responses and environmental aspects also considered (choice of environment, relative present or alone etc.).

3.24.3 Burden

Given the sudden onset of disability as a result of a severe stroke, participants may be vulnerable and adjusting to life after stroke. People with stroke admitted to the SRU participate in active therapy and rehabilitation practice for a minimum of 45 minutes' duration (or as long as tolerated) once a day, a minimum of five days per week as part of their inpatient stay, therefore, participating in the functional standing frame or usual physiotherapy interventions should not have caused any additional burden. However, interviews and outcome assessments with participants are not part of usual stroke care and required additional time. Furthermore, interviews may cover topics that the interviewee may have found distressing or upsetting. They were made aware of this prior to consenting to the interview. At the time of the interview participants were reminded they could pause and/or terminate the interview at any time. Participants were directed to a healthcare professional or a relative for support, if needed, either during or after the interview if required.

For participants who were interviewed in the SRU, members of the research team and clinical care staff were available to support participants, in addition to any relative support, as required. Relatives were informed of the date and time of the interview by the PI for those participants who consented/requested this. For participants who were interviewed at home, the CI informed carer/relatives of the date and time of the interview if the participant consented/requested this. If the participant gave the CI reason to be concerned about their safety during their interview and they lived alone, the CI contacted their General Practitioner.

The sudden change in physical and/or cognitive ability may also impact on the relatives. Relatives may have been obliged to be continually present to support

and assist their loved one during the physiotherapy interventions, increasing their feelings of responsibility and burden. The relative may have wondered if their significant other was being taken care of in their absence and during the trial interventions, which may have created unnecessary/unwanted anxiety. Additionally, the relative may have found the interview upsetting as they too were coming to terms with a sudden change in their significant other.

Other than making available the time required to participate in the interview and focus group, it was not anticipated that physiotherapists would find participating in the trial a burden.

3.24.4 Data protection and patient confidentiality

All investigators and trial site staff were required to comply with the Data Protection Act 1998[326] and the subsequent 2018 Data Protection Act[327] with regards to the collection, storage, processing and disclosure of personal information and to uphold the Act's core principles. The Sponsor is the data custodian and they will store the data for a minimum of five years in a secure location managed by Royal Cornwall Hospitals NHS Trust.

3.24.5 Confidentiality

Individual participant medical information obtained as a result of this trial was and continues to be considered confidential and disclosure to third parties was prohibited with the exceptions noted below.

Participant confidentiality was ensured by using unique trial numbers on all documentation. If information was disclosed during the trial (e.g. during the intervention or control group sessions, trial assessments or interviews) that could pose a risk of harm to the participant or others, the researcher discussed

this with the CI and where appropriate reported accordingly adhering to local policies/procedures.

Identifiable participant details such as name, address and telephone number were stored at each of the four SRUs in line with local data protection and confidentiality guidelines. Additionally, identifiable participant details such as name, address and telephone number were stored securely in the Faculty of Health and Human Sciences, Knowledge Spa, Truro for the purposes of contacting the participants for trial follow-up visits. This data was securely stored in a separate secure cabinet from non-identifiable data such as the CRFs.

Direct quotes will be published in research journals, but they will be anonymised to maintain confidentiality.

3.25 Patient and public involvement

Involving patients and the public in research is intended to benefit the research process by ensuring research is relevant, conducted ethically, participant friendly, and the results made accessible and provided with sensitivity to trial participants and the wider public once the trial is complete[328].

People with severe stroke (weeks, months and years post-stroke), their relatives and clinicians (physiotherapists, OTs, Speech and Language Therapists, doctors) were involved in the development of the trial from the outset through focus groups and one-to-one interviews. The research topic was strongly endorsed as meaningful and relevant by patients, relatives and clinicians. Key priorities of patients were “get up and move straight away” and to “stand and walk as soon as possible” post-stroke. Patients believed it would help them “get back to normal” and “get back to work”.

PPI identified potential difficulties with fatigue and being physically and psychologically overwhelmed in the early stages post-stroke. They suggested trial assessments should be split into two sessions for those that needed it, and that standing time should be slowly built-up because they may get tired. These changes were incorporated into the trial design. PPI also highlighted that those randomly assigned to the control group may be “devastated” about not receiving the intervention, potentially influencing their willingness to participate in the trial. Qualitative interviews explored this to address any impact of this on recruitment and retention. Stroke consultants reviewed eligibility criteria and the trial protocol were reviewed by stroke consultants and local Research and Development teams.

Physiotherapists and OTs working in SRUs highlighted the challenge of identifying a suitable measure of function for people with severe stroke; they were particularly concerned with the ability of outcome measures to identify change from the sub-acute (seven days to six months) to chronic phase (seven months onwards)[3]. They reviewed and discussed the range of available measures, including their psychometric properties. Based on this process, together with a review of the literature, the BI and the Edmans were selected for this feasibility trial.

The development of trial documentation involved significant PPI representation to optimise comprehension and facilitate inclusion of people with varying communication abilities being involved in the trial. Trial documentation was developed using the NIHR resources for stroke researchers which were specifically developed with and for people with aphasia. Two Participant Information Sheets were developed specifically for people with aphasia: an A4 double sided information sheet with pictures only and a multiple paged

information sheet with single line text to accompany pictures. These Participant Information Sheets were reviewed and scrutinised for their suitability for people with aphasia from multiple sources: five people who had a severe stroke (1 month, 9 months, 12 months, 3 and 5 years' post-stroke), all of whom had aphasia; three stroke specialist Speech and Language Therapists; a local communication group for people with aphasia run by a Speech and Language Therapist and a Consumer Group attended by people who have had a stroke based in Bradford run by the Bradford Institute for Health Research.

Participant Information Sheets for relative interviews were reviewed by six relatives. Participant Information Sheets for physiotherapist interview and focus group were reviewed by five physiotherapists. The standard Participant Information Sheet and the multiple page aphasia friendly Participant Information Sheet were reviewed by the Making Reasonable Adjustments Team in Cornwall for readability to ensure trial documentation was aligned with Accessibility Standards for NHS and Social Care providers[329] which came into effect in July 2016.

Two people who had a severe stroke and their relatives were members of the TSC that had overall responsibility for the research. The TSC met regularly throughout the trial to optimise the participants' experience and ensure all aspects of PPI are addressed. They were involved in analysing and interpreting findings of both the systematic review and feasibility trial and commenting on drafts of papers/reports. This optimised the validity of the conclusions from a lay perspective and was intended to highlight findings most relevant to the public. Patients and their relatives were invited to share their perspectives of the interview data to refine the analyses and future interview topic guides. They were involved in formulating the dissemination plan, and disseminating research

findings through links with relevant organisations, joint presentations, and a range of media formats.

PPI who were members of the TSC have and, continue to be supported in several ways. Initial conversations during trial development and funding applications involved information provision as to the purpose and relevance of the research to people who have had a severe stroke. Once funding was in place further discussions were held highlighting the importance of PPI involvement throughout the whole trial and what their role would be (attending meetings, reading/reviewing trial documentation, minutes as well as sharing their thoughts and perspectives on trial design, content and delivery). Recent research suggests that PPI works well if its goals are clear and there are well developed plans for PPI in a trial (for example, membership of a TMG) rather than restricted to general oversight (for example, membership of a TSC)[328]. However, this may be reflective of how much PPI members of the TSC are encouraged and want to be actively involved outside of committee meetings as well as their motivation for being involved in research. I had regular contact with PPI members, providing updates about recruitment and sites opening, changes to the trial protocol or documentations. I acknowledge that the PPI members are supportive of my research as well as me personally which may impact on how successful PPI is in this trial. I do however remain cognisant of the potential burden that their involvement may have in terms of time spent preparing for meetings, travelling to meetings (all PPI members travel from Cornwall to Devon for meetings) and time spent at meetings (approximately two hours).

I have had several discussions with the Peninsula Collaboration for Leadership in Applied Health Research and Care (PenCLAHRC) who have provided access

to online training and Advice Clinics, as well as the INVOLVE booklets which were utilised by our PPI representatives.

From the outset PPI informed the development of this trial, ensuring it reflects the opinions and needs of people with sub-acute severe stroke. The intervention specifically aims to address their stated key priorities of optimising general function, standing and walking. Potential barriers of participation (e.g. fatigue, exercise tolerance, communication difficulties) were carefully considered.

3.26 Philosophical underpinnings

Philosophy is a lens through which we view the world, and which allows researchers to identify knowledge gaps upon which to base research and the method with which the gaps are filled[330]. It is important to declare my philosophical assumptions because they have influenced the development, execution, interpretation, and reporting of this research. Philosophy comprises both ontological and epistemological components.

Ontology aims to understand the nature of the social world and what there is to know about it, of being, of becoming, of existence, and of reality[331]. This has been broadly categorised into realism or idealism. Realism accepts that an external reality exists independent of our beliefs or understanding, whereas idealism assumes that no independent external reality exists[332]. My ontological position of realism was adopted throughout the thesis, due to my consideration that a distinction exists between the way the world is and the interpretation of that world.

Epistemology is concerned with what it means to know; how knowledge can be created, acquired and communicated and the relationship between knowledge

and truth[332]. I adopted the epistemological position of correspondence theory of truth, believing a statement to be true if it matches independent reality. Overall, I aspired to 'empathic neutrality', recognising that although truly value free judgements may not be achieved, assumptions, biases, and values were transparent[332].

This feasibility trial used both quantitative and qualitative methods, thus, subtle changes were occasionally employed to the philosophical assumptions of realism, post-positivism, and pragmatism influencing the 'world view' of this thesis. The qualitative component required an open approach to achieve its aim of capturing experiences of participants, relatives and physiotherapists. Thus, an ontological perspective based on subtle realism was utilised, which recognises the critical importance of participants' own interpretations of the issues researched[333]. Epistemologically the more inductive approach of constructionism was adopted[317].

The RCT was based on pragmatism and post-positivism. The pragmatic paradigm; not committed to any one philosophy or reality, places the "research problem" as central and applies all approaches to understanding the problem[334]. Post-positivism has similar ontological and epistemological beliefs as positivism (objectivism, being impartial, discovering absolute knowledge about and objective reality), post-positivists seek to understand causal relationships and a hypothesis is not proven but simply rejected[333,334]. The systematic review (Chapter 2) was influenced by critical realism and post-positivism, thereby assuming that phenomena are measurable using deductive principles and the scientific model[336]. Both the feasibility RCT and the systematic review were based on the assumption that objective measurements can be used to make inferences about the population of interest[337,338]. The results will not be

considered as objective ‘truths’, however, rather supporting evidence subject to review and consideration[339].

Collectively, the epistemological position adopted in this thesis combined pragmatism and post-positivism.

3.27 Clinician-researcher role

I have been a physiotherapist for 12 years, but leading my research created a new role: clinician-researcher. A clinician-researcher is an individual who conducts research and provides direct patient care[340] although not at the same time and not necessarily for the same organisations.

Several benefits have been identified when clinicians are involved in research: increased clinical relevance of research questions, gaining access to clinical settings to undertake the research, bringing clinical expertise and insider perspectives, having researchers who are trusted by participants that may encourage their participation, and having researchers who are motivated to disseminate applicable findings, continue their commitment to the research[341]. It has been suggested that the clinician role can increase rapport which may result in rich and detailed data[342]. Additionally, clinicians interviewing other clinicians are insider researchers in that they may share at least some understanding of the clinical environment. However, I acknowledge that I do not have experience of delivering the intervention in clinical practice. Thus, I may have understood their language but did not fill in the blanks or make assumptions as this may have led to misinterpretation and consequently lack of exploration of specific issues during interviews.

Several challenges have been identified managing dual perspectives of clinician-researchers: expectations from patient-participants about their clinical

care and the clinician-researcher's natural desire to adopt the role of clinician and respond to the queries of the patient-participant or relatives during assessments/interviews[342]. One of the most pertinent issues was the ethical considerations that included the risk of coercion of participants and the potential blurring of role boundaries between clinician-researcher and participants[342,343]. There was also potential for role confusion which can be external (clarifying my role to others) and internal (feeling conflict and/or tension)[343].

A framework has been developed for dealing with the ethical and practical implications and demands of dual role throughout the research process[343]. I utilised this framework in conjunction with reflexivity and discussions in my supervision sessions to raise ethical and practical issues, grapple with the unavoidability and implications of dual-role and recognise and review both clinical and research obligations and boundaries[342]. This facilitated the balance between privileged access to patients and colleagues with a responsibility for rigorous research methods[344].

Reflexivity was used to place myself and my practice under scrutiny, acknowledging the ethical dilemmas that permeate the research process and impinge on the creation of knowledge[345]. Reflexivity acknowledged how my background and position affected what I chose to investigate, the design and methods, and interpretations[346]. Adopting a reflexive approach throughout my fellowship facilitated creation of a heightened self-awareness facilitating impartiality and rigour in my research.

3.28 Summary

Chapter 3 has presented the research methodology with justification of the design for the trial in relation to the research problem and uncertainties

identified in Chapter 1. Justification of the multi-centre feasibility RCT was presented in terms of why and how this methodology can best answer the trial aims, objectives and research question. Rationale was provided for the qualitative component to ensure the complexity of the intervention was fully evaluated. This chapter acknowledges the pragmatic approach that was adopted and the barriers and facilitators of my new clinician-researcher role.

Chapter 4 presents the quantitative and qualitative results.

Chapter 4 Quantitative results

4.1 Introduction

This chapter presents the quantitative data arising from the physiotherapy sessions for both the intervention (functional standing frame programme) and control (usual physiotherapy) groups during the 3-week intervention period, and the follow-up assessments.

Data presented in this chapter focuses on feasibility objectives: eligibility, consent, recruitment, randomisation and minimisation, acceptability of the intervention, adherence, safety, baseline and demographics of the participants, summary of missing data and blinding. Data from the proposed primary and secondary outcomes will be presented, but the focus of the trial was testing trial procedures and determining acceptability, and not focusing on the outcome of interest.

As stated in the Statistical Analysis plan, analyses are descriptive only.

4.2 Eligibility

Patients admitted to any of the four sites were initially screened for their stroke severity. If patients had been diagnosed with either moderately severe or severe disability post-stroke using the modified Rankin Scale (mRS)[347] the physiotherapists completed a Screening CRF to determine eligibility. A total of 586 patients were admitted across the four SRUs between 1st January 2017 and 30th September 2017 (9 months), n=462 (78.8%) were not eligible and the number and reasons for ineligibility are listed in Tables 4.1a and 4.1b below, and the CONSORT (Figure 4.1).

Reasons not eligible	Number of participants % (n)
Non-stroke	29.43 (136)
Mild stroke	45.67 (211)
Moderate stroke	9.74 (45)
Medically unwell	4.76 (22)
End of life care	4.55 (21)
Erratic behaviour	1.52 (7)
Being transferred out of county	1.30 (6)
Not a new stroke	0.87 (4)
Non-English speaking	0.65 (3)
Additional neurological condition	0.65 (3)
Not meeting nutritional requirements	0.43 (2)
Exceeded weight limit of standing frame	0.43 (2)

Table 4.1a Eligibility on admission

Reasons not eligible	Number of participants % (n)
End of life care	14.29 (2)
Medically unwell	21.42 (3)
Walking independently at baseline	14.29 (2)
Not meeting nutritional requirements	14.29 (2)
Unable to stand due to poor tissue viability	14.29 (2)
Neurological condition	7.14 (1)
Orthopaedic impairment	7.14 (1)
Being discharged out of county	7.14 (1)

Table 4.1b Eligibility post-screening

Seventy-three potential participants were screened but n=14 (19.2%) were deemed not eligible and n=13 potential (17.8%) participants were deemed eligible but were not consented (n=2 died, n=7 declined, n=4 staff shortage). A total of 46 participants subsequently provided consent; a consent rate of 78%. Reasons why seven eligible potential participants did not want to participate in the trial were not captured in the CRFs.

4.3 Consent

Ability to provide consent was 63.0% based on 29 participants providing informed consent. Seventeen (37.0%) consultees declared informed consent.

Two participants provided consent themselves, and their consultee also declared consent. Reasons for this were not captured on the Screening CRF.

4.4 Recruitment

A CONSORT[348] flow diagram (Figure 4.1) has been used to present a summary of the trial recruitment and retention pathway. It displays the number of potential participants admitted to the four SRUs, number eligible and ineligible patients, number of participants who provided consent and completed baseline assessments, number randomised to each of the two groups, number of participants who completed the 3-week intervention period and the follow-up assessments, and number of withdrawals.

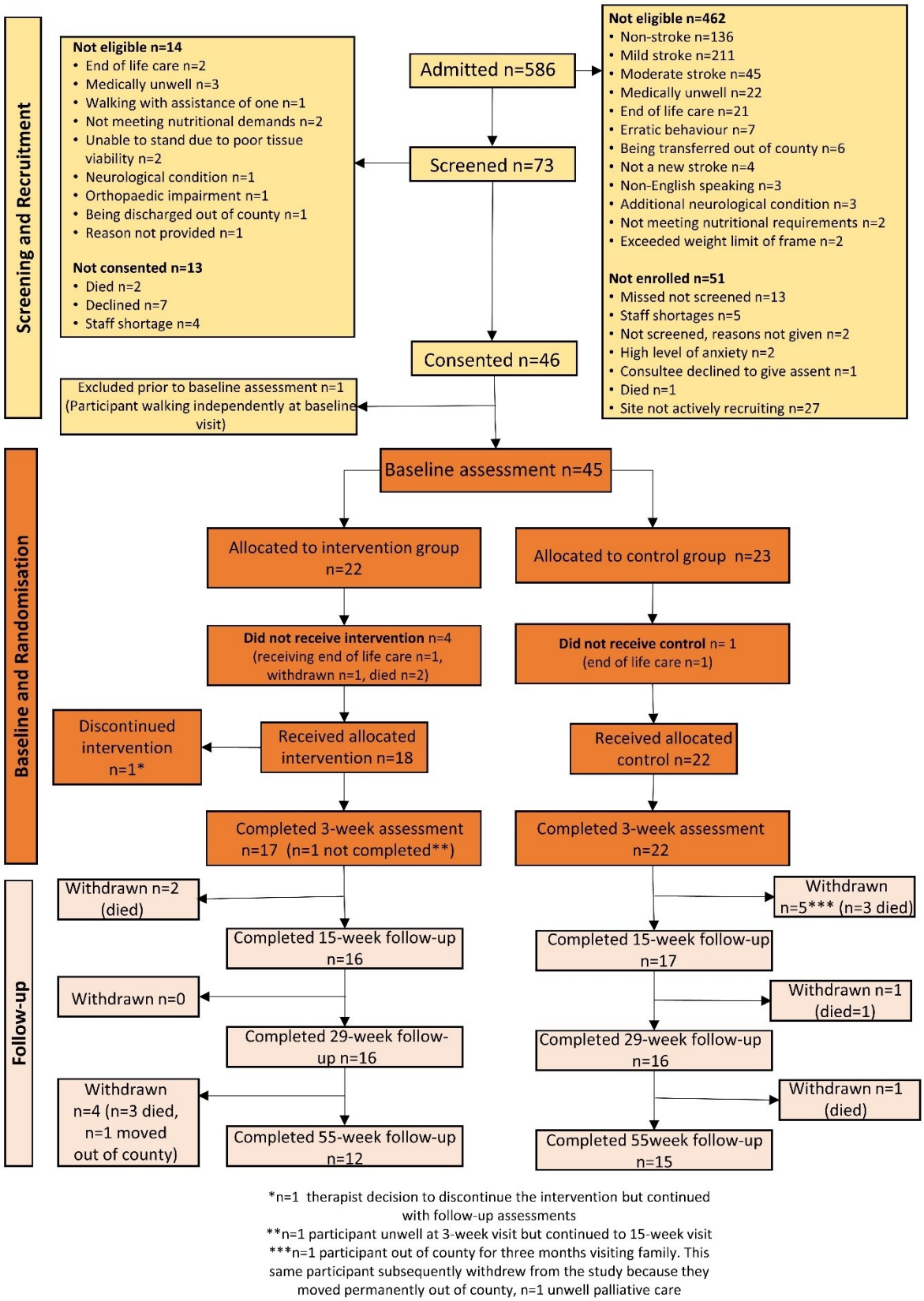


Figure 4.1 CONSORT flow diagram

4.4.1 Recruitment rate

The recruitment target was 50 participants in 12 months. Due to delays with Health Research Authority approvals and subsequent approval for capacity and capability, the recruitment period was 10 months with staggered opening of sites. The first two sites opened 5th December 2016 but due to staff shortages over the Christmas holidays they did not commence logging admissions and actively recruiting until 2nd January 2017, thus data for the recruitment period was captured for nine months only. The third site opened 10th February 2017 and the fourth site opened 26th June 2017 due to organisational restructuring of stroke services. A total of 45 participants over 10 months were recruited, 90% of the target.

The first participant was recruited on 9th January 2017. An average 4.2 participants per month for 12 months across all four sites was predicted, and the actual number of participants recruited in 10 months was 4.5 participants per month (Figure 4.2). If recruitment had continued for the planned 12 months, the target of 50 would have been reached at 11.2 months. The percentage recruitment rate was 7.6% per month, calculated by dividing the number of participants recruited per month (4.5) by the number of participants who met the inclusion criteria (n=59) multiplied by 100.

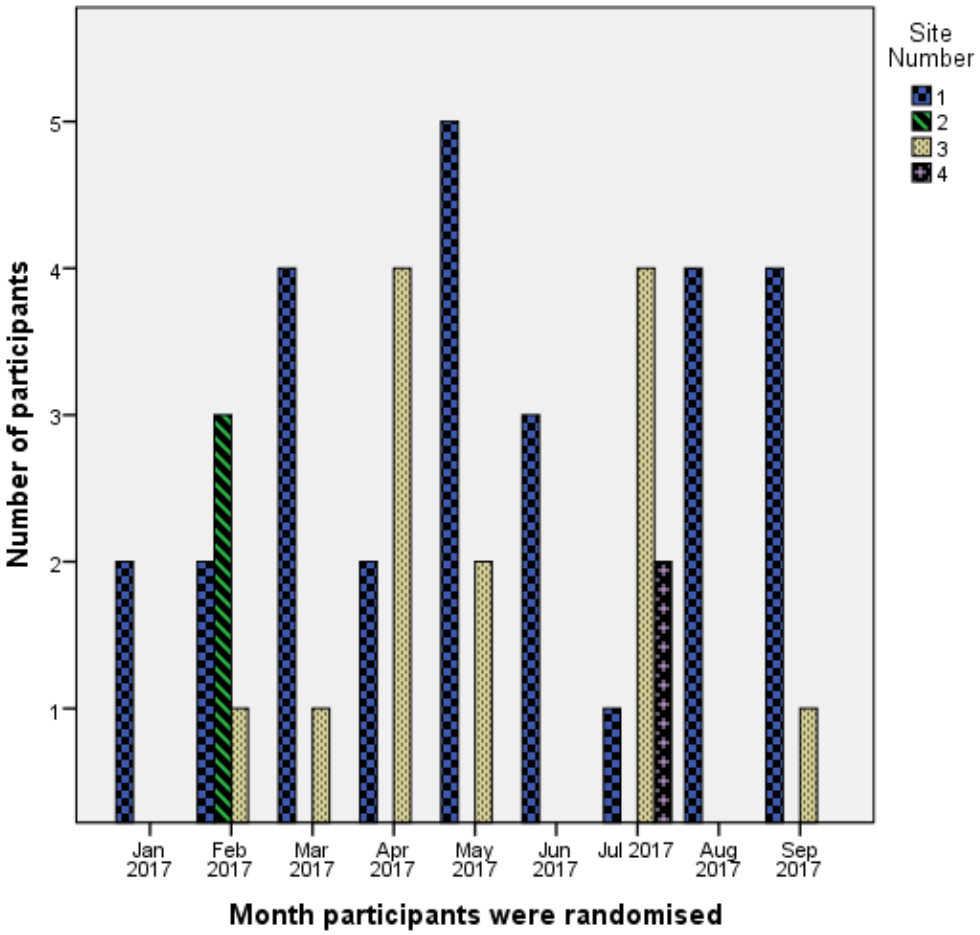


Figure 4.2 Recruitment for all four sites

The number of beds and staffing affected recruitment. The number of beds varied among sites: site 1: 21 beds; site 2: 9 beds; site 3: 15 beds; site 4: 18 beds, which resulted in different staff:patient ratios but broadly aligned with recommendations[3,349]. However, sites with smaller number of beds had less ability to manage staff absences/vacancies. This was evident at site 2, which stopped recruiting in March due to significant staffing issues. Clinical Research Network staff were involved in recruiting at site 4, but this did not appear to have a significant impact on numbers recruited at this site.

Of the n=46 participants who consented, one was not randomised because they were walking independently at their baseline visit. The numbers recruited per site/month is shown in Figure 4.2 This highlights that total recruitment varied

with site (site 1 n=27, site two n=3, site three n=14 (only n=13 randomised), site four n=2)). The highest recruiter was the site that was local and most known to the CI. The percentage of participants screened who provided consent varied among sites (site 1 50.9%, site 2 100%, site 3 9.3% and site 4 100%). However, 51 were not enrolled in the trial as highlighted in the CONSORT diagram and this also varied among sites with sites 1 and 3 (the largest recruiters) showing lower numbers of non-enrolment than site 2 (site 1 11.76%, (n=6), site 2 70.6%, (n=36), site 3 17.6%, (n=9), site 4 0% (n=0)).

4.5 Randomisation and minimisation

A total of 45 participants were randomised; n=22 into the intervention group (intervention) and n=23 into the control group (control). Table 4.2 provides details on the minimisation characteristics in both groups. Both groups were similar for fatigue and orthostatic hypotension.

Characteristic	Intervention % (n) [within allocation n=22]	Control % (n) [within allocation n=23]
Fatigue		
0-3 (no or minimal fatigue)	18.2 (4)	17.4 (4)
4-10 (fatigue)	81.8 (18)	82.6 (19)
Orthostatic Hypotension		
% with orthostatic hypotension at randomisation	18.2. (4)	13.0 (3)
% without orthostatic hypotension at randomisation	81.8 (18)	87.0 (20)

Table 4.2 Minimisation characteristics in allocated groups

4.6 Baseline and demographic data

Baseline and demographic data is summarised in Tables 4.3a (Demographic data), 4.3b (Pre-stroke disability status and medical and surgical conditions). 4.3c (Pre-stroke medical and surgical conditions for the intervention group) and 4.3d (Disability status post-stroke). Forty-five participants were recruited to the

trial with an overall mean age of 80.3 years (age range 51-96 years), n=1 in their 50s, n=7 in their 60s, n=10 in their 70s, n=17 in their 80s and n=10 in their 90s. Both groups were similar in age range. The age range in the control group was 60-94 years (mean age 78.9 years). The age range in the intervention group was 51-96 years (mean age 81.7 years).

There were more females (57.8%) in the trial than males (42.2%), but both groups were similar in this respect with 39.1% (n=10) males in the control group and 45.5% (n=9) in the intervention group (Table 4.3a).

	Intervention [n=22]	**Control** [n=23]	**All** [n=45=]
Age in years, Mean (SD) [range]	81.7 (11.7) [51-96]	78.9 (10.5) [60-94]	80.3 (11.1) [51-96]
Gender % (n)			
Male	45.5 (10)	39.1 (9)	42.2 (19)
Female	54.5 (12)	60.9 (14)	57.8 (26)
Weight in kg, mean (SD) [range]	69.3 (13.9) [38.0-94.8]	77.3 (17.3) [43.0-112.0]	73.6 (16.0) [38.0-112.0]
Marital Status % (n)			
Single	0 (0)	13.0 (3)	6.7 (3)
Married or in a civil partnership	50.0 (11)	21.7 (5)	35.6 (16)
Separated	0.0 (0)	0.0 (0)	0.0 (0)
Divorced	4.5 (1)	4.3 (1)	4.4 (2)
Widowed	31.8 (7)	60.9 (14)	46.7 (21)
Missing	13.6 (3)	0.00 (0)	6.7 (3)
Place of Residence % (n)			
Lives at home	86.4 (19)	91.3 (21)	88.9 (40)
Lives in residential care	9.1 (2)	4.3 (1)	6.7 (3)
Other	4.5 (1)	4.3 (1)	4.4 (2)
Living Arrangements % (n) (not mutually exclusive, more than one option could be ticked)			
Alone	22.7 (5)	65.2 (15)	44.4 (20)
Spouse/Partner	50.0 (11)	21.7 (5)	35.6 (16)
Warden controlled flat	4.5 (1)	0.0 (0)	2.2 (1)
Parent(s)	4.5 (1)	0.0 (0)	2.2 (1)
Children under 18	4.5 (1)	0.0 (0)	2.2 (1)
Children over 18	18.2 (4)	8.7 (2)	13.3 (6)
Other family	0.0 (0)	8.7 (2)	4.4 (2)
Non-family	9.1 (2)	0.0 (0)	4.4 (2)

Employment Status % (n)			
In employment or self-employed	4.5 (1)	4.3 (1)	4.4 (2)
Retired	90.9 (20)	91.3 (21)	91.1 (41)
Unemployed	4.5 (1)	4.3 (1)	4.4 (2)

Table 4.3a Demographic data

Pre-stroke disability (modified Rankin Scale (mRS)) and mobility varied between groups (Table 4.3b). The control group had higher (30.4%) percentage of participants with slight disability (mRS 1) versus 9.1% in the intervention group, and there were more participants with pre-stroke moderate disability (mRS4) in the intervention group (22.7%) compared to the control group (13.0%). In contrast, pre-stroke, more participants in the intervention group walked without an aid (54.5% n=12 equivalent to mRS 1-3). In the control group (26.1% n=6) walked without an aid. More participants in the control group walked with an aid or physical assistance (73.9%, n=17) versus 45.5% (n=10) in the intervention group; equivalent to mRS4-5.

The incidence of medical and surgical conditions (Table 4.3b) were mostly similar between groups, with a high number of people across both groups with coronary heart disease, hypertension/hypotension and COPD/asthma. More participants in the control group had diabetes and depression/anxiety. Five participants had dementia or Alzheimer's listed as "other" medical conditions; n=3 in the control group and n=2 in the intervention group.

Stroke classification differed between groups with more TACS in the intervention group (72.7%) and more PACS and LACS in the control group (65.2%). Middle cerebral artery stroke was the most common stroke (17%), nearly twice the number of which were in the control group. Days since stroke

were similar in both groups, ranging from 0-36 days. Aphasia was more prevalent in the intervention group (59.1 %). The prevalence of orthostatic hypotension was similar in both groups (17.4% in the control group and 13.6% in the intervention group) and the prevalence of fatigue was high but similar in both groups (43.5% tired and 34.8% really tired in the control group versus 50.0% and 27.3% in the intervention group).

	Intervention [n=22]	**Control** [n=23]	**All** [n=45]
Pre-stroke modified Rankin Scale % (n)			
0 (no symptoms)	40.9 (9)	13.04 (3)	26.7 (12)
1 (no significant disability)	9.1 (2)	34.80 (8)	22.2 (10)
2 (slight disability)	13.6 (3)	30.43 (7)	22.2 (10)
3 (moderate disability)	9.1 (2)	8.69 (2)	8.9 (4)
4 (moderately severe disability)	22.7 (5)	13.04 (3)	17.8 (8)
5 (severe disability)	4.5 (1)	0.0 (0)	2.2 (1)
6 (dead)	0.0 (0)	0.0 (0)	0.0 (0)
Pre-stroke mobility status % (n)			
Walking without an aid	54.5 (12)	26.1 (6)	40.0 (18)
Walking with an aid	41.0 (9)	73.9 (17)	57.8 (26)
Walking with physical assistance	4.5 (1)	0.0 (0)	2.2 (1)
Mechanical aid with assistance	0.0 (0)	0.0 (0)	0.0 (0)
Medical and surgical conditions % (n) (not mutually exclusive, more than one option could be ticked)			
Osteoarthritis – has/had this condition	19.0 (8)	13.6 (6)	16.3 (14)
Osteoarthritis – ongoing at study entry	20.0 (8)	11.3 (6)	15.1 (14)
Joint replacement – has/had this condition	11.9 (5)	4.5 (2)	8.1 (7)
Joint replacement – ongoing at trial entry	0.0 (0)	0.0 (0)	0.0 (0)
Osteoporosis – has/had this condition	2.4 (1)	2.3 (1)	2.3 (2)
Osteoporosis – ongoing at trial entry	2.5 (1)	1.9 (0)	2.2 (2)
Coronary heart disease/Hypertension/ Hypotension – has/had this condition	35.7 (15)	36.4 (16)	36.0 (31)
Coronary heart disease/Hypertension/	35.0 (14)	30.2 (16)	32.3 (30)

Hypotension – ongoing at trial entry			
COPD/Asthma – has/had this condition	4.8 (2)	6.8 (3)	5.8 (5)
COPD/Asthma – ongoing at trial entry	5.0 (2)	5.7 (3)	5.4 (5)
Diabetes – has/had this condition	4.8 (2)	13.6 (6)	9.3 (8)
Diabetes – ongoing at trial entry	4.8 (2)	13.6 (6)	9.3 (8)
Depression/anxiety – has/had this condition	4.8 (2)	11.4 (5)	8.1 (7)
Depression/anxiety – ongoing at trial entry	2.5 (1)	9.4 (5)	6.5 (6)
TIA – has/had this condition	9.5 (4)	6.8 (3)	8.1 (7)
TIA – ongoing at trial entry	0.0 (0)	0.0 (0)	0.0 (0)
Epilepsy/seizure – has/had this condition	2.4 (1)	2.3 (1)	2.3 (2)
Epilepsy/seizure – ongoing at trial entry	2.5 (1)	1.9 (1)	2.2 (1)
Neurological condition – has/had this condition	4.8 (2)	2.3 (1)	3.5 (3)
Neurological condition – ongoing at trial entry	5.0 (2)	0.0 (0)	2.2 (2)
Other* – ongoing at trial entry	22.5 (9)	28.3 (15)	25.8 (24)
Had previous strokes (%)	18.2 (4)	21.7 (5)	20.0 (9)
For those with previous stroke, median (IQR) number of strokes	1.0 (2)	0.0 (0)	

*Polymyalgia rheumatica, leg ulcers, bowel cancer, malignant melanoma, iron deficient anaemia, necrotising scleritis, giant cell arteritis, diverticulitis, atrial fibrillation, hypercholesterolemia, hypothyroidism, Crohn's disease, dementia, Korsakoff dementia, Alzheimer's, ankylosing spondylitis, peripheral neuropathy, carpal tunnel syndrome, gall stones, chronic kidney disease, migraines, bronchiectasis, mediastinal lymphadenopathy, rheumatoid arthritis, macular degeneration, cataracts, Fuchs dystrophy, glaucoma.

Table 4.3b Pre-stroke disability status and medical and surgical conditions

Most participants in the intervention group had multiple morbidities (Table 4c). Four participants had one co-morbidity; 11 had two, three had three and two had four.

Participant number	N and description of morbidity/multi-morbidities for intervention group participants
01005	2 (osteoarthritis and previous stroke)
01008	3 (osteoarthritis, joint replacement and coronary heart disease/hyper- or hypotension
01009	4 (coronary heart disease/hyper- or hypotension, depression/anxiety, diabetes, joint replacement)
01010	4 (COPD/Asthma, coronary heart disease/hyper- or hypotension, diabetes, osteoarthritis
01013	1 (coronary heart disease/hyper- or hypotension)
01014	3 (coronary heart disease/hyper- or hypotension, osteoarthritis, osteoporosis)
01015	2 (coronary heart disease/hyper- or hypotension)
01018	no data
01019	2 (coronary heart disease/hyper- or hypotension, TIA)
01020	2 (coronary heart disease/hyper- or hypotension, TIA)
01024	2 (joint replacement, osteoarthritis)
01042	3 (coronary heart disease/hyper- or hypotension, joint replacement, TIA)
01043	2 (coronary heart disease/hyper- or hypotension, TIA)
01051	no data
01054	2 (coronary heart disease/hyper- or hypotension, COPD/Asthma)
01055	1 (osteoarthritis)
02003	2 (coronary heart disease/hyper- or hypotension, osteoarthritis)
03007	1 (osteoarthritis)
03011	2 (coronary heart disease/hyper- or hypotension, epilepsy/seizure)
03012	1 (coronary heart disease/hyper- or hypotension)
03014	2 (depression/anxiety, neurological condition)
04002	2 (coronary heart disease/hyper- or hypotension, joint replacement)

TIA, transient ischaemic attack; COPD, chronic obstructive pulmonary disease

Table 4.3c Pre-stroke medical and surgical conditions for the intervention group

For post-stroke mobility status (Table 4.3d), over half of the participants required a hoist for transfers, with slightly more in the control group (60.9%) than in the intervention group (40.9%), but the severity of stroke (mRS) was similar in both groups.

	Intervention [n=22]	Control [n=23]	All [n=45]
Current mobility status % (n) (mutually exclusive but n=1 in control group ticked hoist and electronic stand aid)			
Hoist	40.9 (9)	60.9 (14)	51.1 (23)
Transfer board	0.0 (0)	0.0 (0)	0.0 (0)
Handling belt	0.0 (0)	0.0 (0)	0.0 (0)
Electronic standing aid	22.7 (5)	8.7 (2)	15.6 (7)
Mechanical standing aid	36.4 (8)	30.4 (7)	33.3 (15)
How many people required?			
One person	0.0 (0)	4.35 (1)	2.2 (1)
Two people	100.0 (22)	91.30 (21)	95.6 (43)
Two to three people (variable)	0.0 (0)	4.35 (1)	2.2 (1)
Stroke severity % (n) (option to complete NIHSS or mRS therefore, only 22 out of 45 completed)			
NIHSS at time of screening			
0 (no stroke symptoms)	0.0 (0)	0.0 (0)	0.0 (0)
1-4 (minor stroke)	4.54 (1)	0.0 (0)	2.2 (1)
5-15 (moderate stroke)	13.63 (3)	21.7 (5)	17.8 (8)
16-20 (moderate to severe stroke)	22.73 (5)	17.4 (4)	20.0 (9)
21-42 (severe stroke)	9.1 (2)	8.7 (2)	8.9 (4)
mRS at time of screening			
0 (no symptoms)	0.0 (0)	0.0 (0)	0.0 (0)
1 (no significant disability)	0.0 (0)	0.0 (0)	0.0 (0)
2 (slight disability)	0.0 (0)	0.0 (0)	0.0 (0)
3 (moderate disability)	0.0 (0)	0.0 (0)	0.0 (0)
4 (moderately severe disability)	77.3 (17)	82.6 (19)	80.0 (36)
5 (severe disability)	22.7 (5)	17.4 (4)	20.0 (9)
6 (dead)	0.0 (0)	0.0 (0)	0.0 (0)
Stroke classification (between groups) % (n)			
TACS (total anterior circulation stroke)	72.7 (16)	30.4 (7)	51.1 (23)
PACS (partial anterior circulation stroke)	13.6 (3)	39.1 (9)	26.7 (12)
POCS (posterior circulation stroke)	9.1 (2)	4.3 (1)	6.7 (3)
LACS (lacunar syndrome)	4.5 (1)	26.1 (6)	15.6 (7)

Lesion location (% and n within allocation) (not mutually exclusive n=2 in control group and n=3 in the intervention group had multiple lesion locations ticked)			
Cortical			
Middle cerebral artery	27.3 (6)	50.0 (11)	38.6 (17)
Frontal	13.6 (3)	0.0 (0)	6.8 (3)
Sub-cortical			
Thalamus	0.0 (0)	0.0 (0)	0.0 (0)
Basal ganglia	4.5 (1)	13.6 (3)	9.1 (4)
Midbrain	0.0 (0)	0.0 (0)	0.0 (0)
Pons	0.0 (0)	0.0 (0)	0.0 (0)
Medulla	0.0 (0)	0.0 (0)	0.0 (0)
Cerebellum	4.5 (1)	4.5 (1)	4.5 (1)
Brain stem	0.0 (0)	0.0 (0)	0.0 (0)
Parietal	9.1 (2)	4.5 (1)	6.8 (3)
Temporal	0.0 (0)	0.0 (0)	0.0 (0)
Occipital	13.6 (3)	4.5 (1)	9.1 (4)
Other*	13.6 (3)	18.2 (4)	15.9 (7)
*(small vessel disease, haemorrhage or haemorrhagic transformation)			
Stroke sub-type % (n) (these options were linked with lesion location above and not mutually exclusive)			
Lacunar	0.0 (0)	13.6 (3)	6.8 (3)
Anterior cerebral artery	0.0 (0)	9.1 (2)	4.5 (2)
Posterior cerebral artery	0.0 (0)	0.0 (0)	0.0 (0)
Basilar artery	0.0 (0)	0.0 (0)	0.0 (0)
Cerebellar artery	4.5 (1)	4.3 (1)	4.5 (2)
Carotid artery	0.0 (0)	0.0 (0)	0.0 (0)
Other	0.0 (0)	0.0 (0)	0.0 (0)
Missing	0.0 (0)	4.3 (1)	2.2 (1)
Prevalence of aphasia % (n)	59.1 (13)	47.8 (11)	53.3 (24)
Prevalence of orthostatic hypotension % (n)	13.6 (4)	17.4 (3)	15.6 (7)
Prevalence of fatigue % (n)			
0-3 (not tired, or a little tired)	22.7 (5)	21.7 (5)	22.2 (10)
4-6 (tired)	50.0 (11)	43.5 (10)	46.7 (21)
7-10 (really tired)	27.3 (6)	34.8 (8)	31.1 (14)
Days since stroke admitted to Stroke Rehabilitation Unit, median (range) [IQR]	10.0 (0-31) [11]	6.0 (0-36) [10]	7.0 (0-36) [11.0]
Days since stroke informed consent received, median (range) (IQR)	11.0 (3-32) [10.0]	15.0 (5-25) [13]	13.50 (3-32) [11.0]
Days since admission to Stroke Rehab Unit consent received, median (range) [IQR]	3.0 (1-9) [4.0]	3.0 (1-22) [4.0]	3.0 (1-22) [4.0]

Table 4.3d Disability status post-stroke

4.7 Adherence

4.7.1 Number of sessions

Adherence for this feasibility trial was defined as completing the three-week intervention with a minimum of five and maximum of seven sessions per week (minimum total of 15 sessions and maximum total of 21 sessions). None of the participants completed all 21 sessions and only eight participants across the two groups completed 15 or more sessions over the three weeks: three (13.6%) in the intervention group and five (21.7%) in the control group. Thus, during this trial participants were not receiving the recommended number of sessions for their stroke rehabilitation[3]. The mean number of sessions overall for the intervention group was 8.14 (9.0 median), compared to 10.54 (12.00 median) in the control group, ranging from one to 16 for both groups during the 3-week physiotherapy period. The session number frequency distribution for both groups is summarised in Figure 4.3.

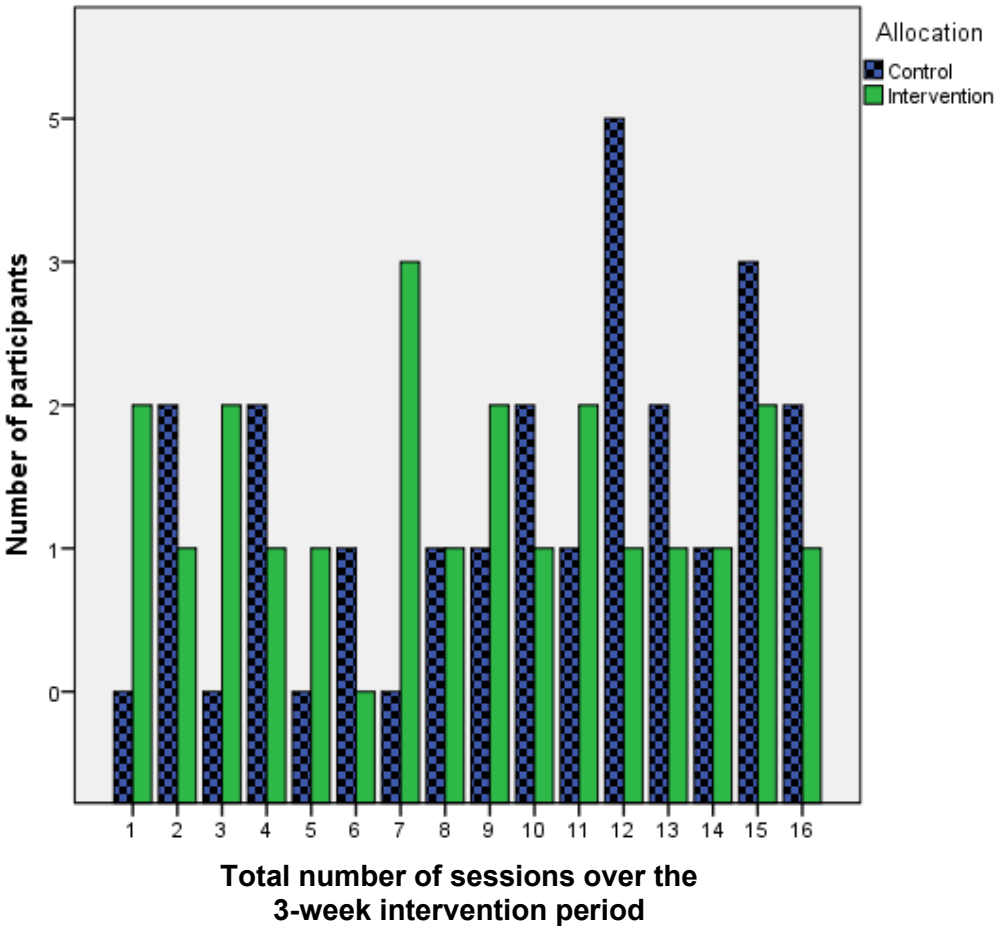


Figure 4.3 Number of sessions completed out of 21 sessions for both groups during the 3-week intervention period

The number of sessions completed per week varied in both groups (Figure 4.4). In the intervention group, one of the three participants who completed 15 sessions, consistently completed five sessions per week in each of the three weeks. Four participants in the control group consistently completed a minimum of five sessions per week over the three weeks. Number of sessions per week over the three weeks for the other three participants ranged from one to seven in the control group and three to six.

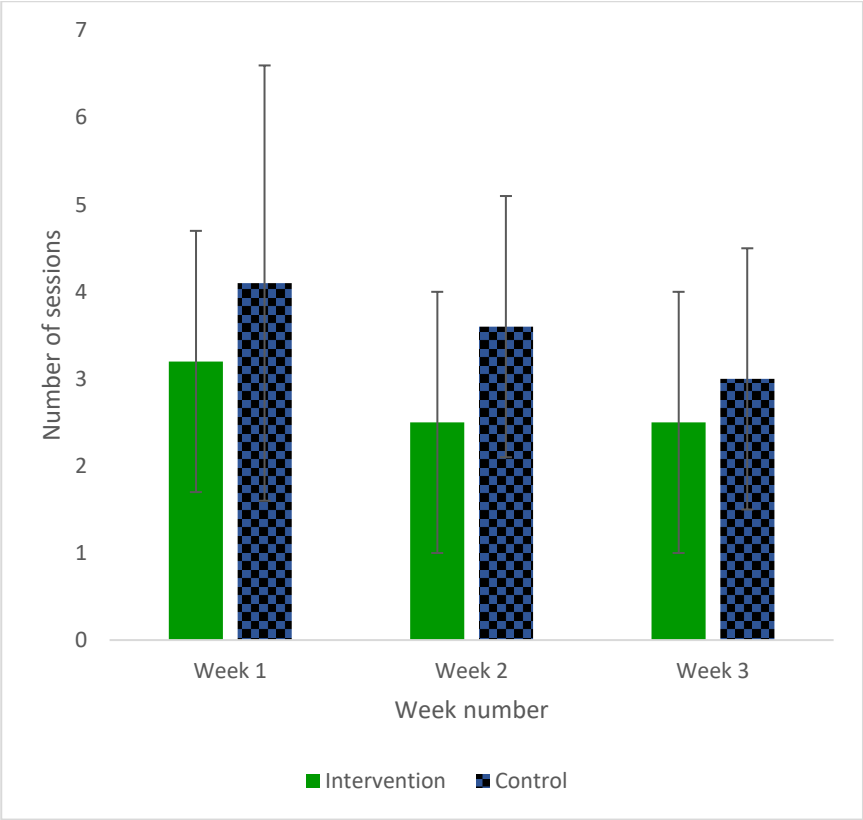


Figure 4.4 Mean number ± SD (error bars) of sessions completed per week for both groups during the 3-week physiotherapy period

In summary, the mean total number of sessions across the three weeks per week in the intervention group was 8.2 (week one 3.1, week two 2.5, week three 2.6) and 10.5 in the control group (week one 4.2, week two 3.5, week three 2.8.0) (Figure 4.4).

4.7.2 Session duration, standing time and sit to stand repetitions

The mean duration of sessions in the intervention group was 36.6 minutes (±10.6 standard deviation (SD)), the median 40.0 minutes compared with 39.40 minutes (± 18.8 SD), 45.0 minutes (median) in the control group. Figure 4.5 summarises the session duration for both groups.

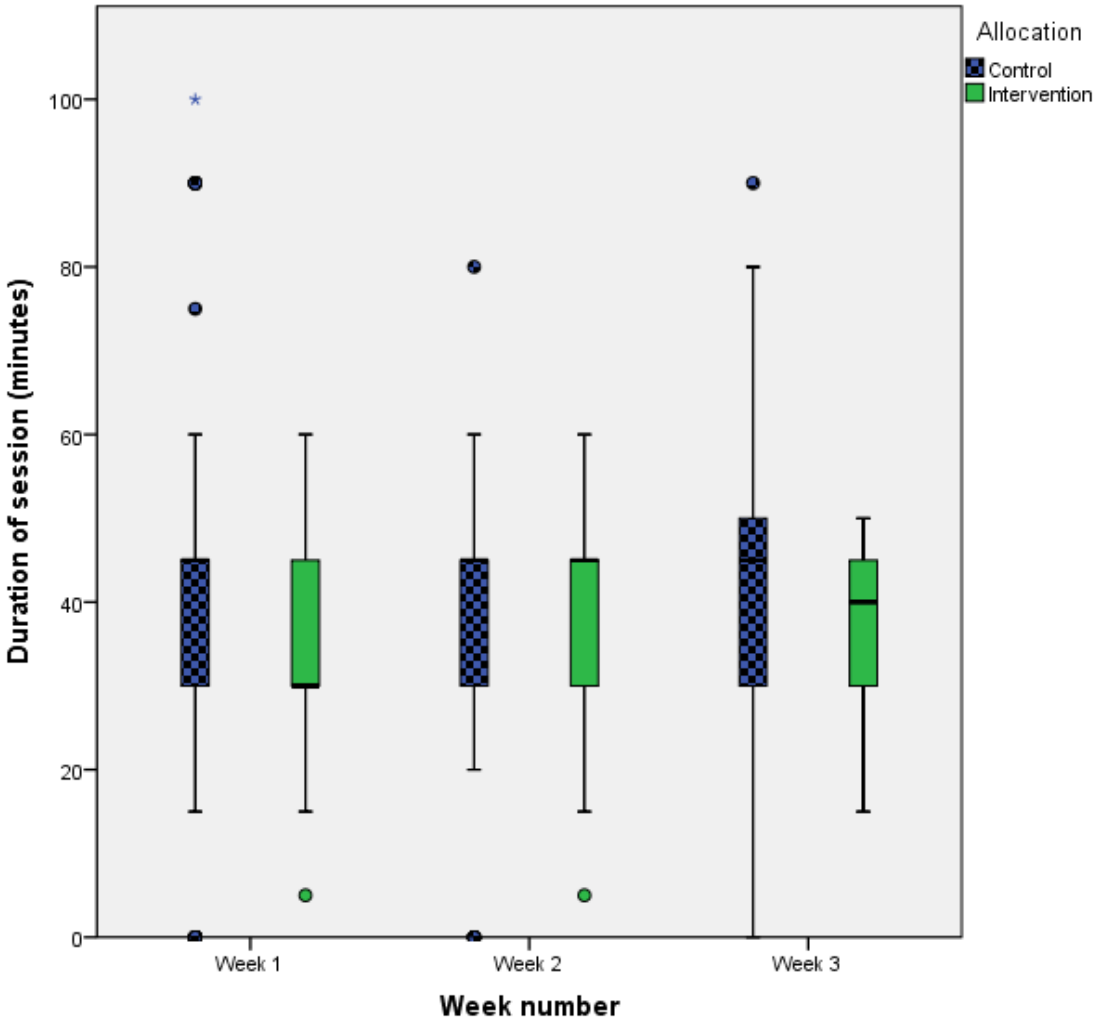


Figure 4.5 Median, quartiles and extreme values duration of session for both groups

The target duration of standing was 30 minutes or to increase the duration of standing by 30% each session. The mean duration of standing when the participant completed a session was 12.52 minutes (±8.8 SD), median 11.00. Figure 4.6 shows the duration of stand for the intervention group across each week. Prevalence of standing (and other treatment activities) for the control group were captured, but not the duration for each activity. Therefore, the duration of standing for the control group is not known.

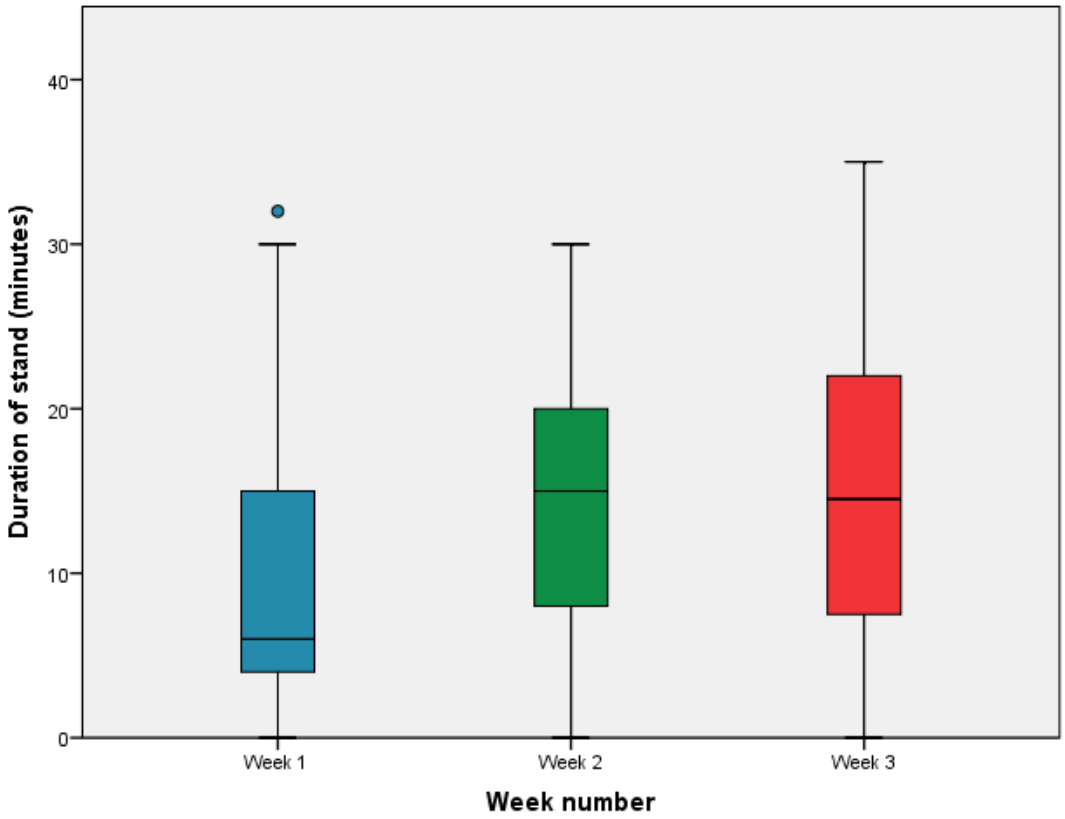


Figure 4.6 Median, quartiles and extreme values duration of stand for the intervention group

The frequency distribution of standing duration is summarised in Figure 4.7. Two participants stood for longer than the 30 minutes (n=1, 32 minutes, n=1 36 minutes), reasons for which were not captured in the CRF. A minimum of 30 minutes standing was achieved in n=10 sessions (n=6 participants). Most participants stood for ≤20 minutes, with 15 and 20 minutes being the most common standing duration,

Not all participants in the intervention group stood in their sessions. Five participants across eight sessions did not achieve any standing during their documented intervention session. Reasons for not standing during these eight sessions were not captured. Reasons for sessions not being completed are shown in Figure 4.13.

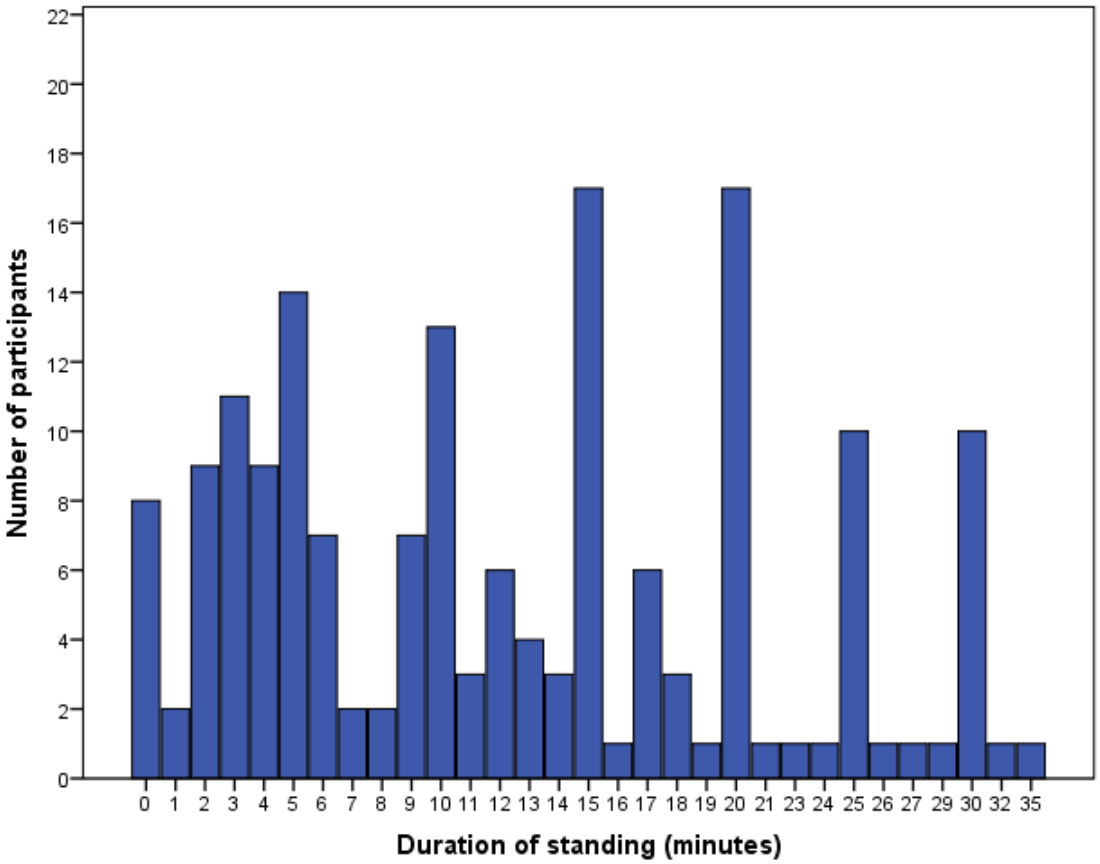


Figure 4.7 Duration of standing for the intervention group

The target session time for the intervention group was 45 minutes during which time participants were aiming to stand for 30 minutes or increase the duration of standing by 30% each session up to the 30 minutes maximum standing time. As highlighted in Figure 4.8 the relationship between duration of standing and duration of session is skewed to the right; that is longer session durations tended to be associated with longer durations of standing.

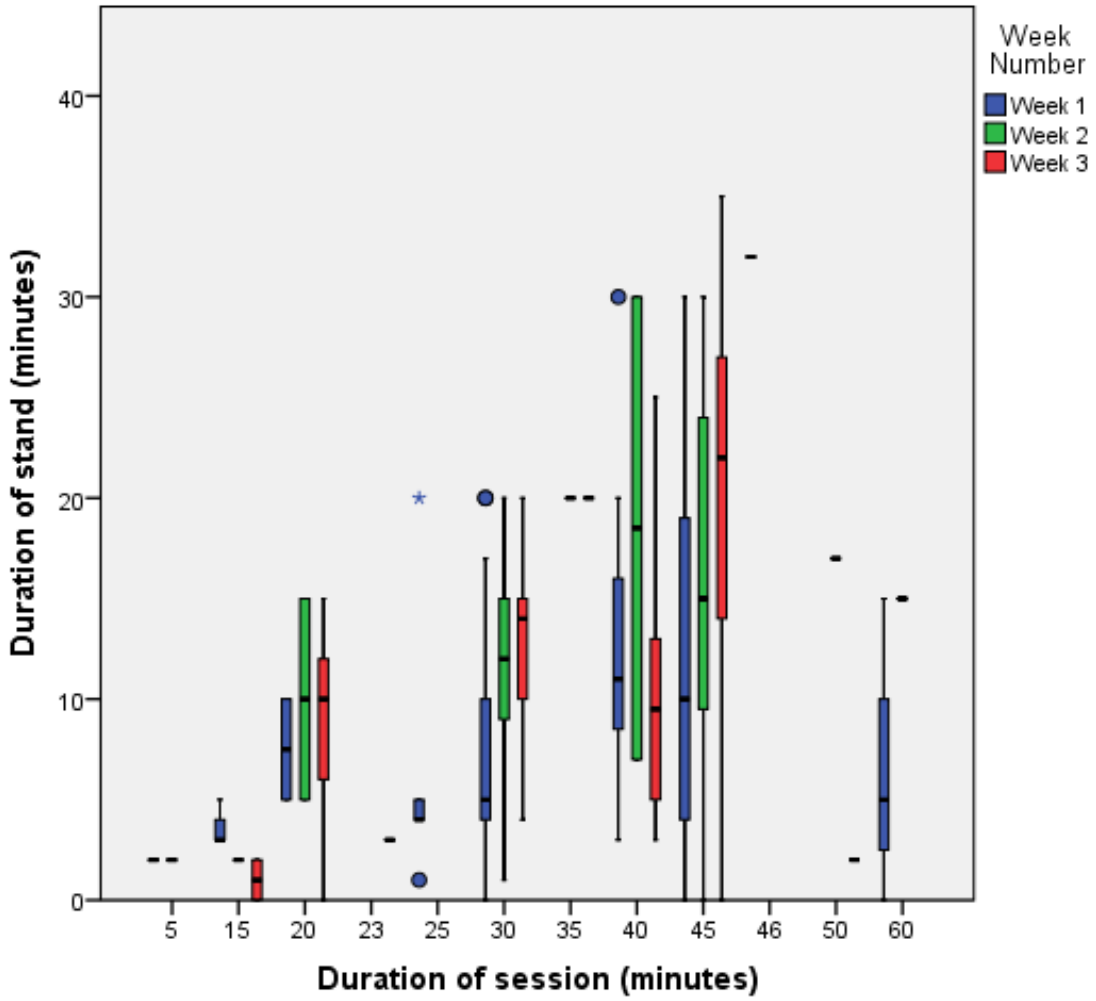


Figure 4.8 Median, quartiles and extreme values for the duration of session and number of minutes in standing for the intervention group (not per participant)

As stated above, the aim was for participants to stand for 30 minutes per day, five times per week, or increase the duration of standing by 30% each session up to the 30 minutes maximum standing time. Looking at a percentage change is difficult because many sessions had zero minutes of standing, thus calculations cannot be made with a denominator of zero. This is because participants were not aligned to start standing on the same day, therefore, some started on a Friday, and not all physiotherapists worked weekends/bank holidays, and some participants were unwell/unavailable and did not stand.

However, it was possible to calculate the change per week using 150 minutes (30 minutes, five times per week) as the minimum target duration of standing. Figure 4.9 shows the percentage change per week and highlights variability in the data with some participants increasing their duration of standing over time, however, some participants decreased their time in standing.

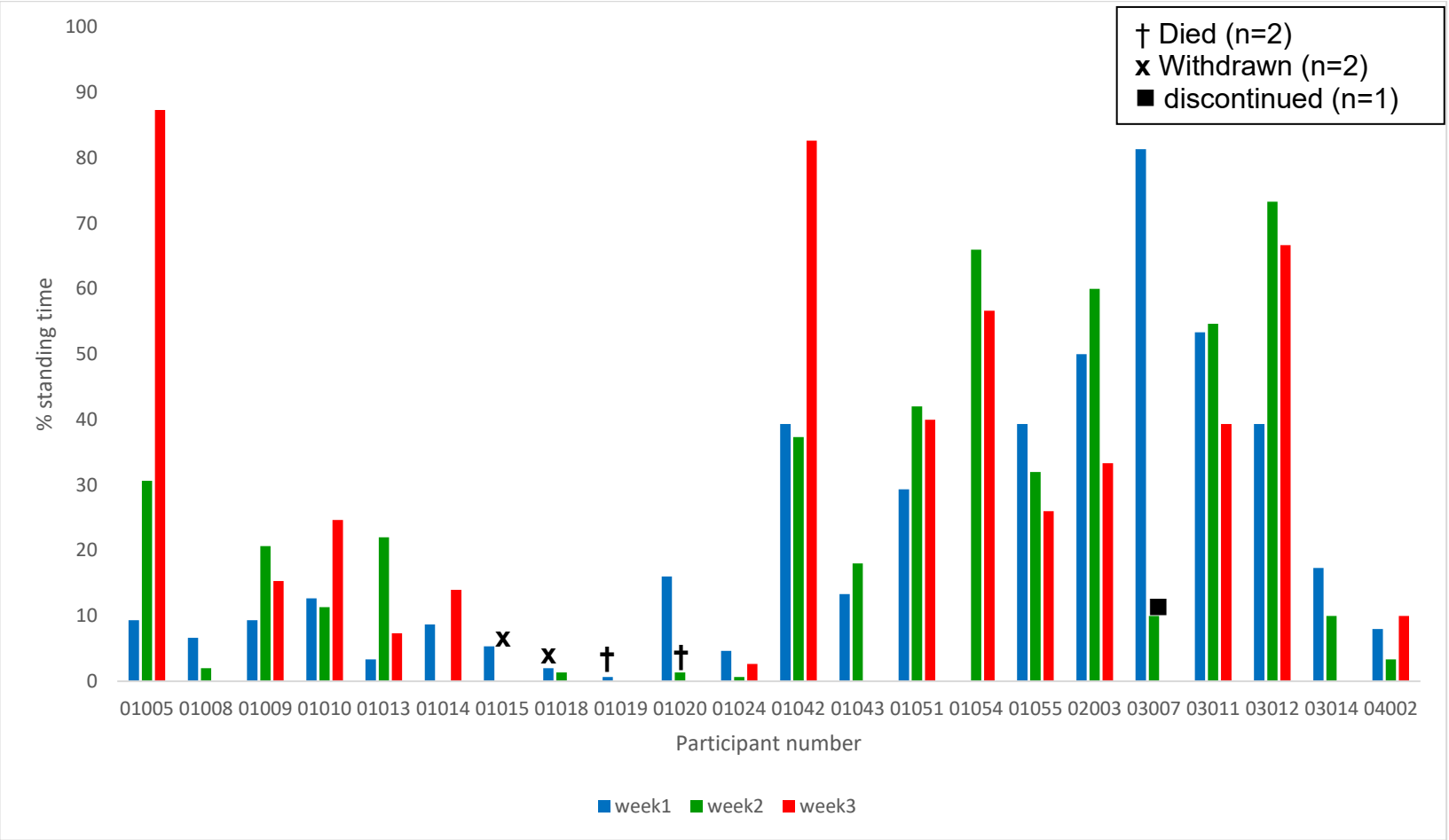


Figure 4.9 Percentage change in standing time per week for the intervention group

The mean number of sit to stand repetitions within a session was 4.64 (±3.9 SD), median 3.00, range 0-20. The number of sit to stand repetitions across sessions is summarised in Figure 4.10. The frequency distribution of the number of sit to stand repetitions across the three weeks is summarised in Figure 4.11 and the percentage change per week in Figure 4.12.

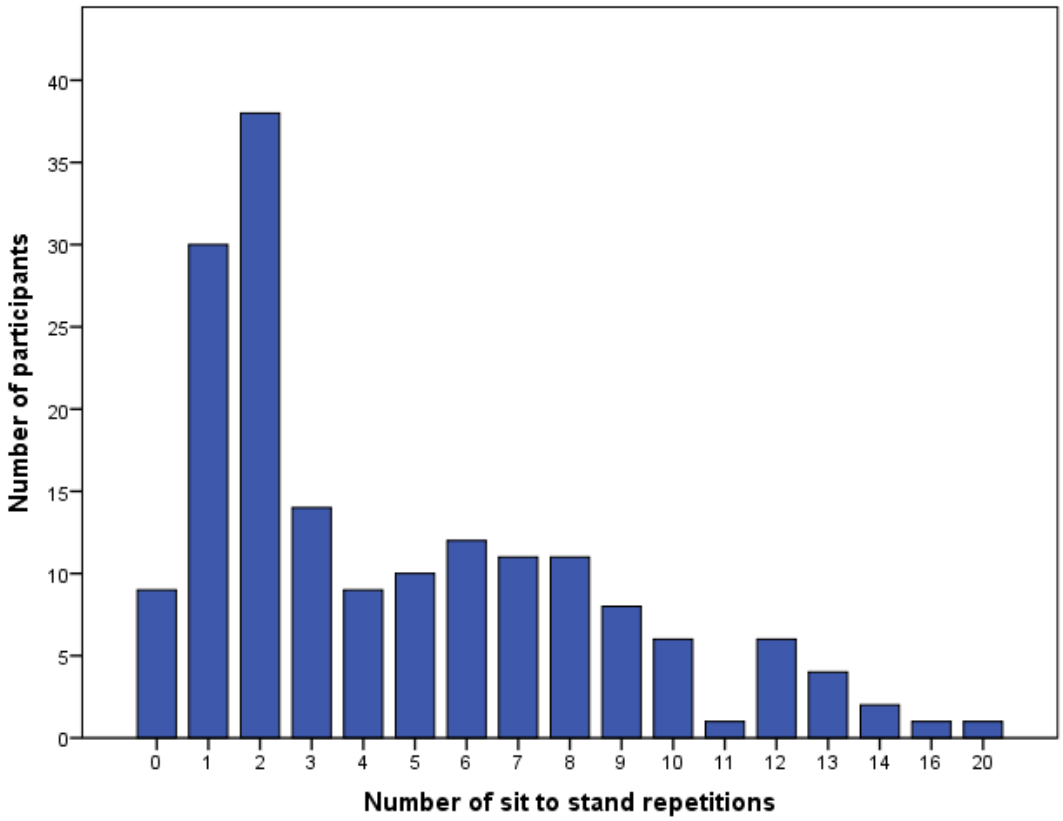


Figure 4.10 Number of sit to stand repetitions within a session for the intervention group

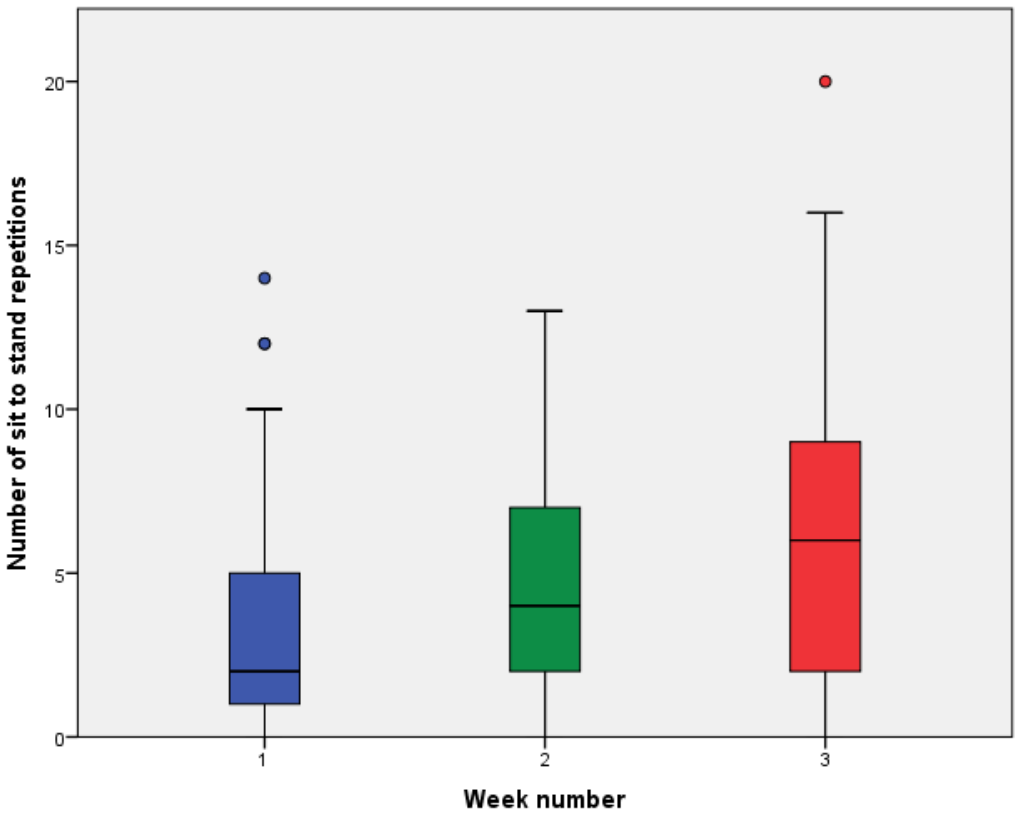


Figure 4.11 Median, quartiles and extreme values of sit to stand repetitions per week for each of the 3 weeks for the intervention group

The target number of sit to stand repetitions was 8-12 with a graded increase of 30% in each session, as per standing duration. Unfortunately, it is not known whether the adherence of sit to stand repetitions was due to participant ability or adherence by physiotherapists to the protocol. Additionally, the work instruction did not prescribe a starting position, e.g., perched or normal chair height.

100% represents the minimum target, 40 repetitions of sit stand per week for the three weeks. Three participants reached the target level.

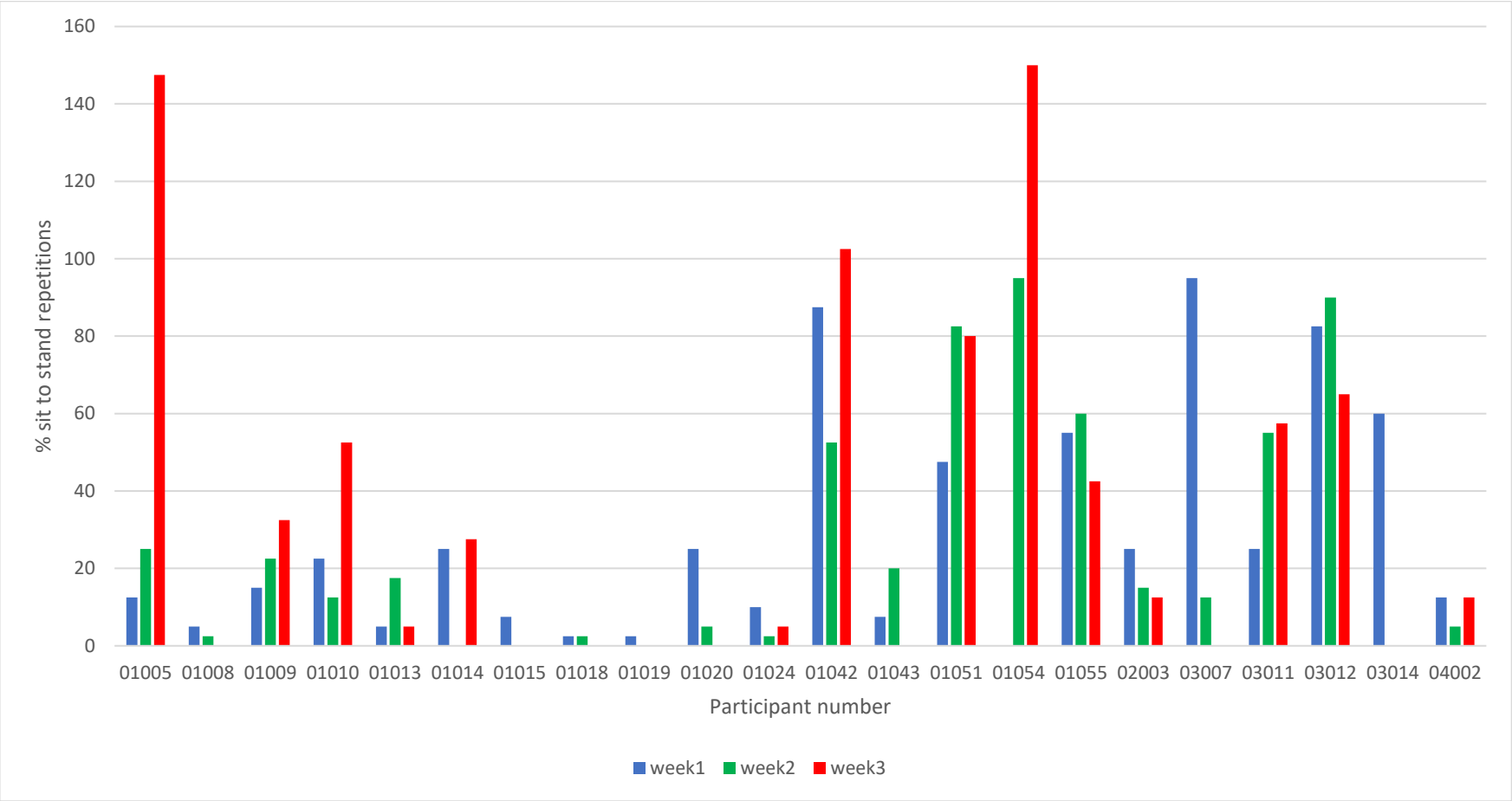


Figure 4.12 Percentage change of sit to stand repetitions per week for the intervention group

4.7.3 Reasons for non-adherence

Out of the 945 potential sessions (45 participants x 21 sessions each), 429 (45.4%) were completed, 503 (53.2%) were not completed and 13 (1.4%) were records missing. The most common reasons for incomplete sessions in total were staffing (n=264, 51.2%) and patients being unwell (n=97, 18.8%). A total of 22 participants declined n=53 sessions in total (n=32 sessions in the intervention group and n=21 in the control group). The percentage of the different reasons for not completing a session are summarised in Figures 4.13 and 4.14.

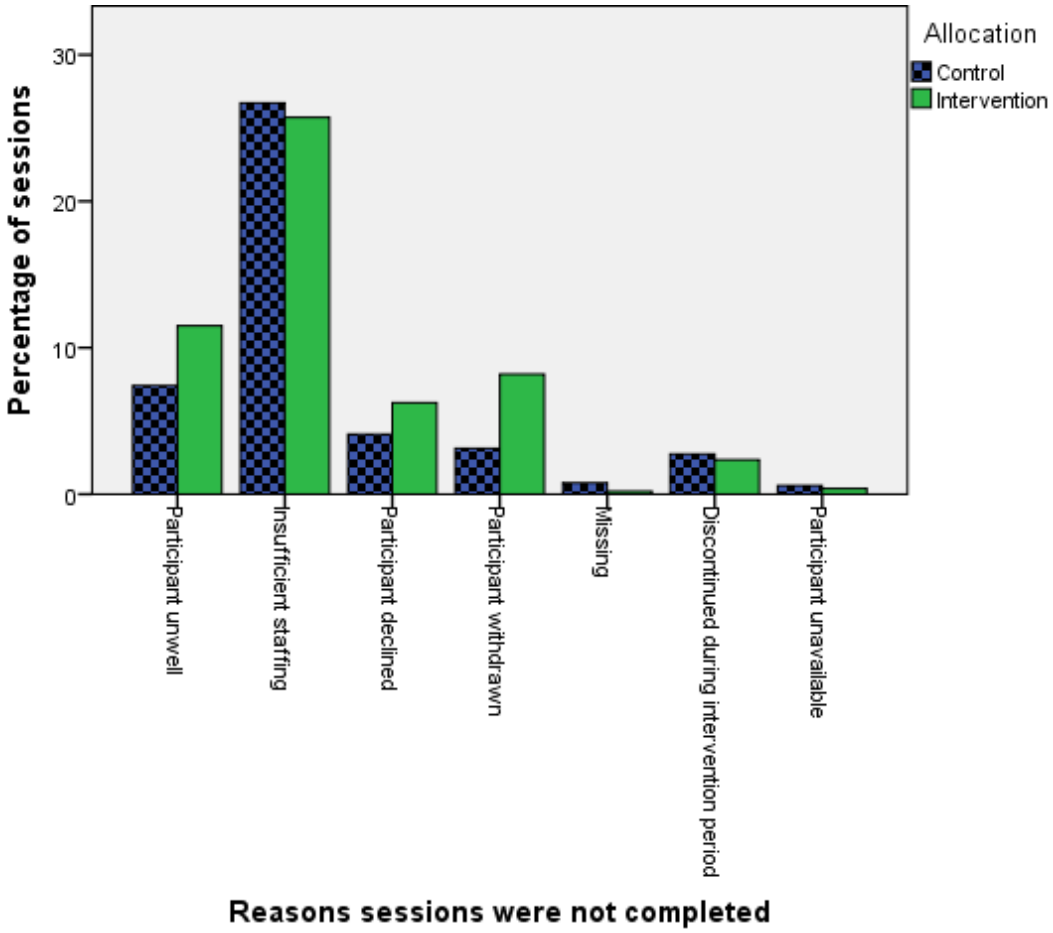


Figure 4.13 Reasons for non-adherence across both groups during the 3-week physiotherapy period

One participant discontinued the intervention following recommendation from a physiotherapist. This participant continued with their follow-up visits at all timepoints.

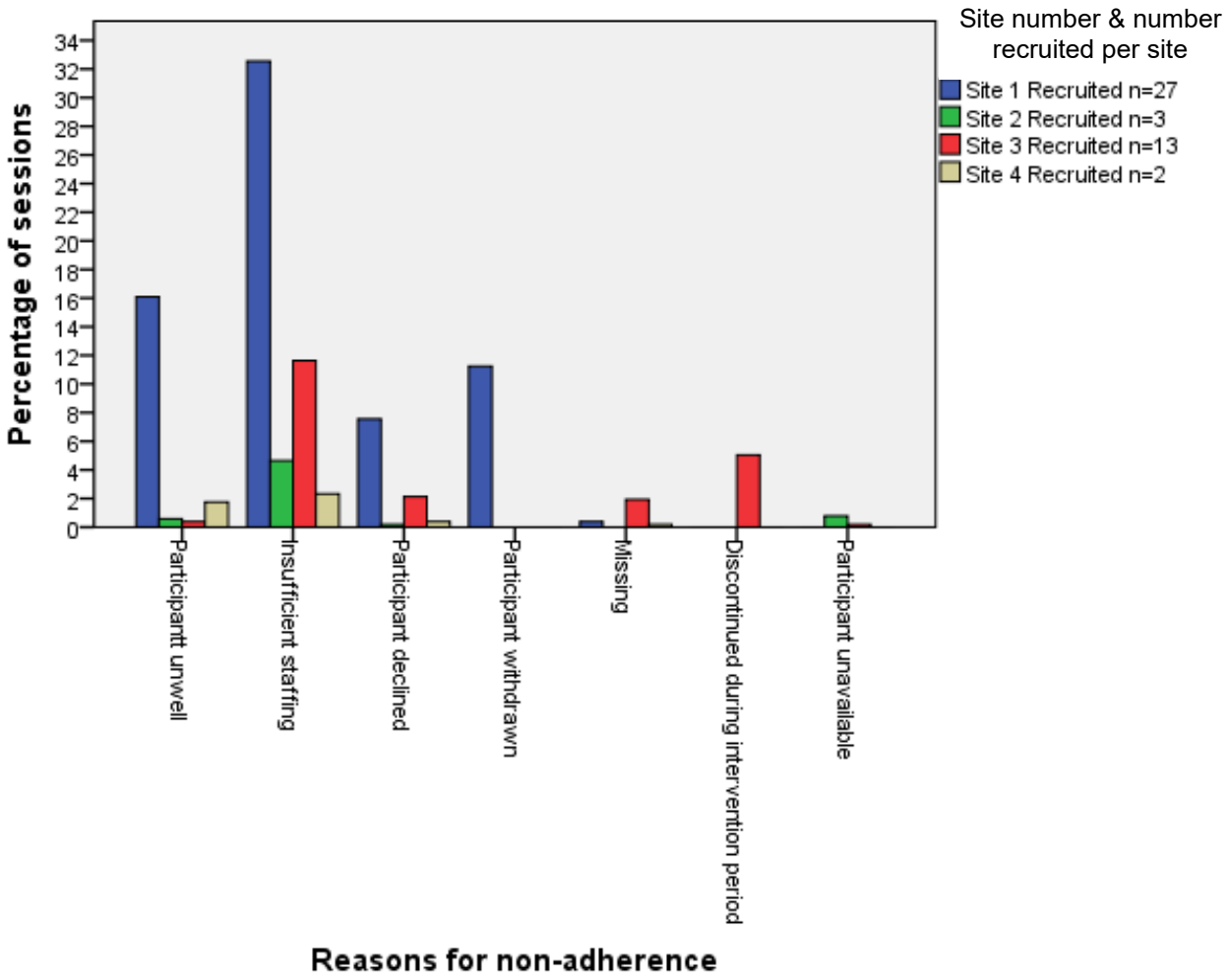


Figure 4.14 Reasons for non-adherence by site during the 3-week physiotherapy period

4.7.4 Relationship between age, stroke severity and duration in standing for the intervention group

There were no clear trends between the duration of standing and stroke severity when controlling for age (Figure 4.15) or gender (Figure 4.16) in the intervention group. However, in both figures, except for one participant, participants with very severe stroke stood for less time than the majority of participants with a

moderately severe stroke. In Figure 4.15, as age increases the duration of standing decreases in participants with very severe stroke (mRS5).

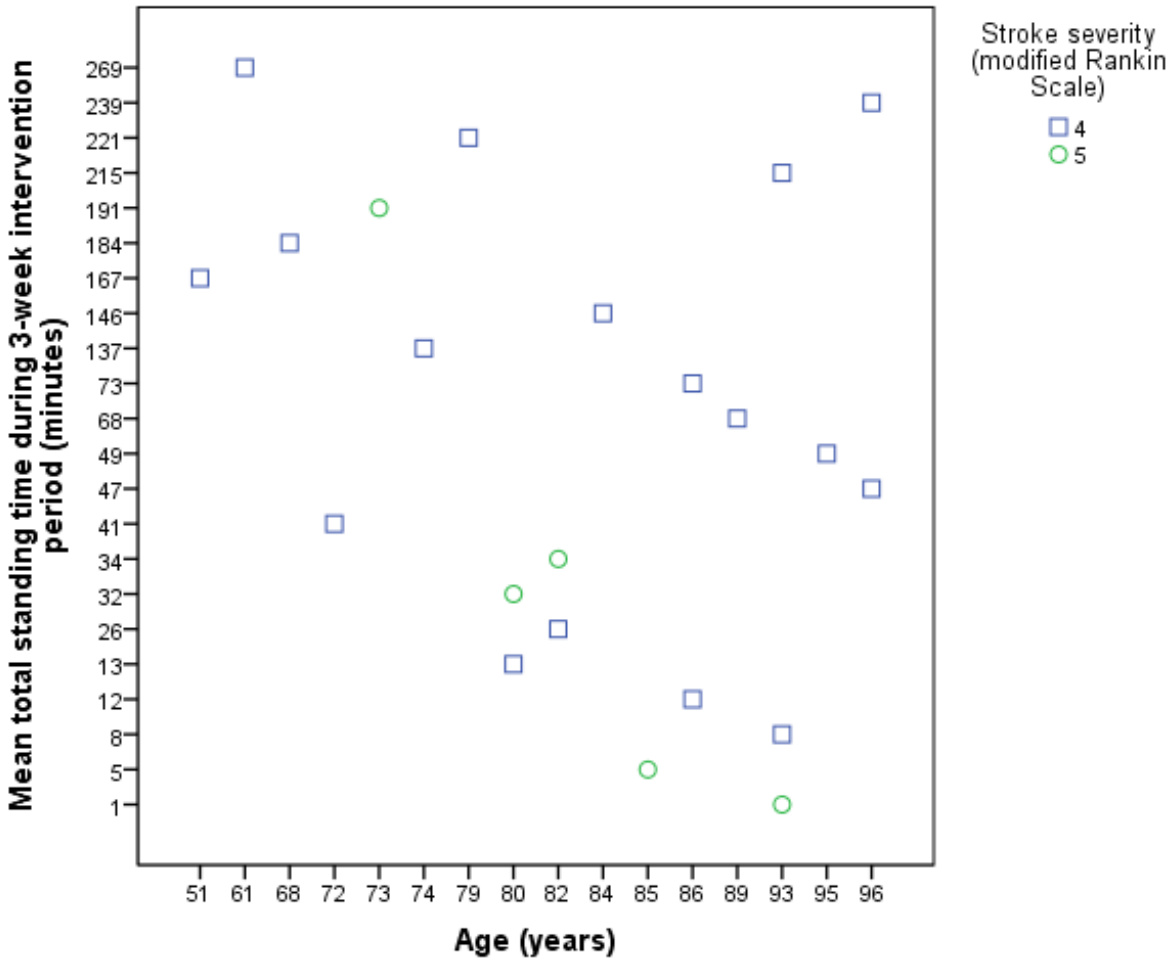


Figure 4.15 Relationship between age, stroke severity and duration in standing for the intervention group

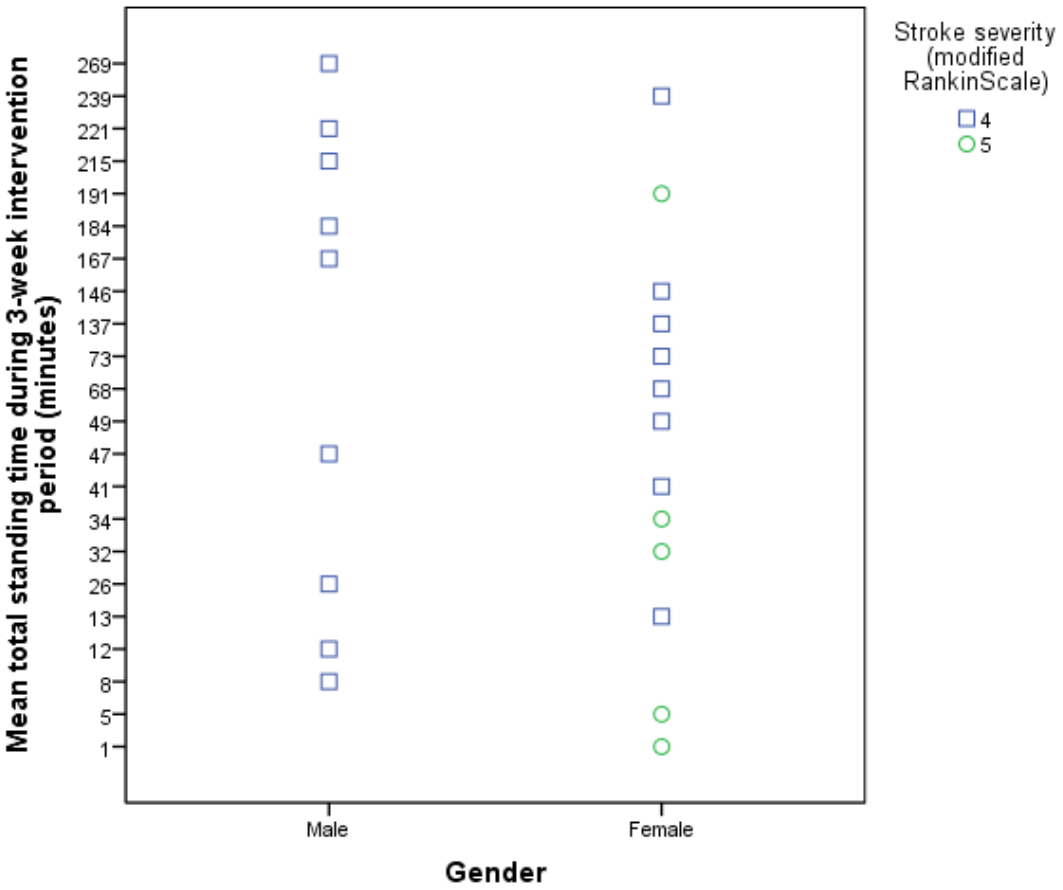


Figure 4.16 Relationship between gender, stroke severity and duration in standing for the intervention group

The CRF did not require physiotherapists to document the exact number of minutes participants in the intervention group spent undertaking usual physiotherapy activities after using the standing frame. The CRF captured the number of minutes in standing and the duration of session. Data in Figure 4.17 was calculated by subtracting the minutes in standing from the duration of session (minutes). Reasons participants received more than 15 minutes of usual physiotherapy were not captured. The duration of usual physiotherapy in the intervention group varied: mean 35.8 minutes, ±SD 16.1 minutes, range 3-100 minutes.

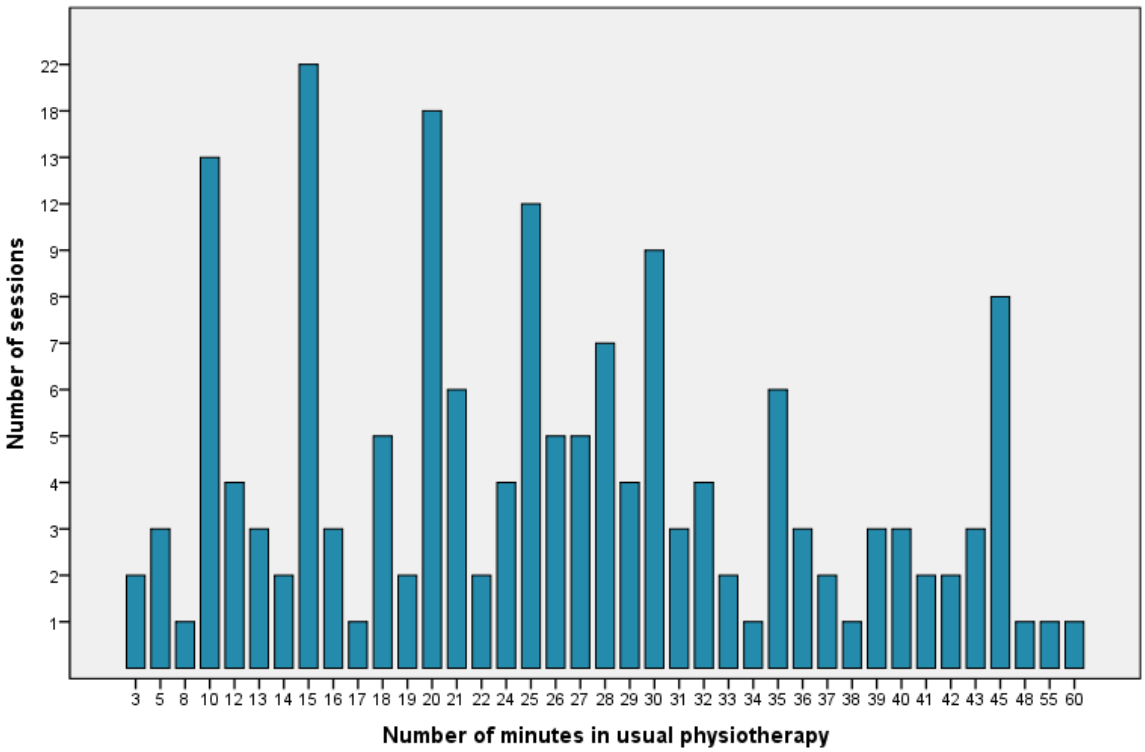


Figure 4.17 Adherence to 15 minutes of usual physiotherapy in the intervention group

Participants in the intervention group were required to complete 30 minutes of prolonged standing, 8-12 repetitions of sit to stand, and 15 minutes of usual physiotherapy for each of their 21 sessions, or a minimum of 15 sessions. This was not achieved by any of the participants. Only six sessions (n=4 participants) met the target of 30 minutes of standing, 15 minutes of usual physiotherapy and eight or more sit to stand repetitions.

In summary, no participants achieved complete adherence (Table 4.4). However, overall adherence did not incorporate a graded increase of sit to stand repetitions or weekly adherence criteria allowing for progression of standing time and sit to stand repetitions over time, therefore, it is unsurprising complete adherence was not achieved by any participant.

Complete adherence* for intervention group	% (n)
Yes	0.0 (0)
No	100.0 (22)

*minimum 5 sessions per week, 30 minutes of standing and 15 minutes of usual physiotherapy and 8-12 sit to stand repetitions

Table 4.4 Complete adherence for the intervention group

Table 4.5 shows the breakdown of adherence by site. Two sites (2 and 3) had participants (n=3) complete 15 or more sessions during the 3-week intervention period. However, only one participant completed five sessions per week every week, the other two participants completed different number of sessions per week (n=1 week 1 five, week 2 four and week 3 six, and week 1 six, week 2 three and week 3 six sessions). None of the participants adhered to the target duration of standing or sit to stand repetitions.

	Stroke severity	Site 1 % (n) [this site recruited n=27]	Site 2 % (n) [this site recruited n=3]	Site 3 % (n) [this site recruited n=13]	Site 4 % (n) [this site recruited n=2]
Number of participants at this site who completed minimum 15 or maximum 21 sessions	mRS 4	3.7 (1)	0.00 (0)	15.40 (2)	0.00 (0)
	mRS 5	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Number of participants at this site who achieved 30 minutes in standing	mRs 4	11.11 (3)	33.33 (1)	15.40 (2)	0.00 (0)
	mRS 5	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Number of sessions at this site in which participants achieved 30 minutes in standing	mRs 4	3.60 (4) [out of 111 completed sessions]	(1) [out of 11 completed sessions]	12.90 (5) [out of 39 completed sessions]	0.00 (0)
	mRS 5	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Number of participants at this site who completed 8-12 (or more) sit to stand repetitions	mRS 4	22.2 (6)	0.00 (0)	30.80 (4)	0.00 (0)
	mRS 5	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Number of sessions at this site in which participants achieved 8-12 (or more) sit to stand repetitions	mRs 4	17.1 (19) [out of 111 completed sessions]	0.00 (0)	38.5 (15) [out of 39 completed sessions]	0.00 (0)
	mRS 5	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)

Table 4.5 Adherence by site for intervention group

It was anticipated that fatigue and OH may impact completion of intervention sessions. Figure 4.18 shows the relationship between fatigue and OH measured during their intervention sessions and the number of minutes participants were able to stand during these sessions. Most participants with fatigue and OH spent less time in standing.

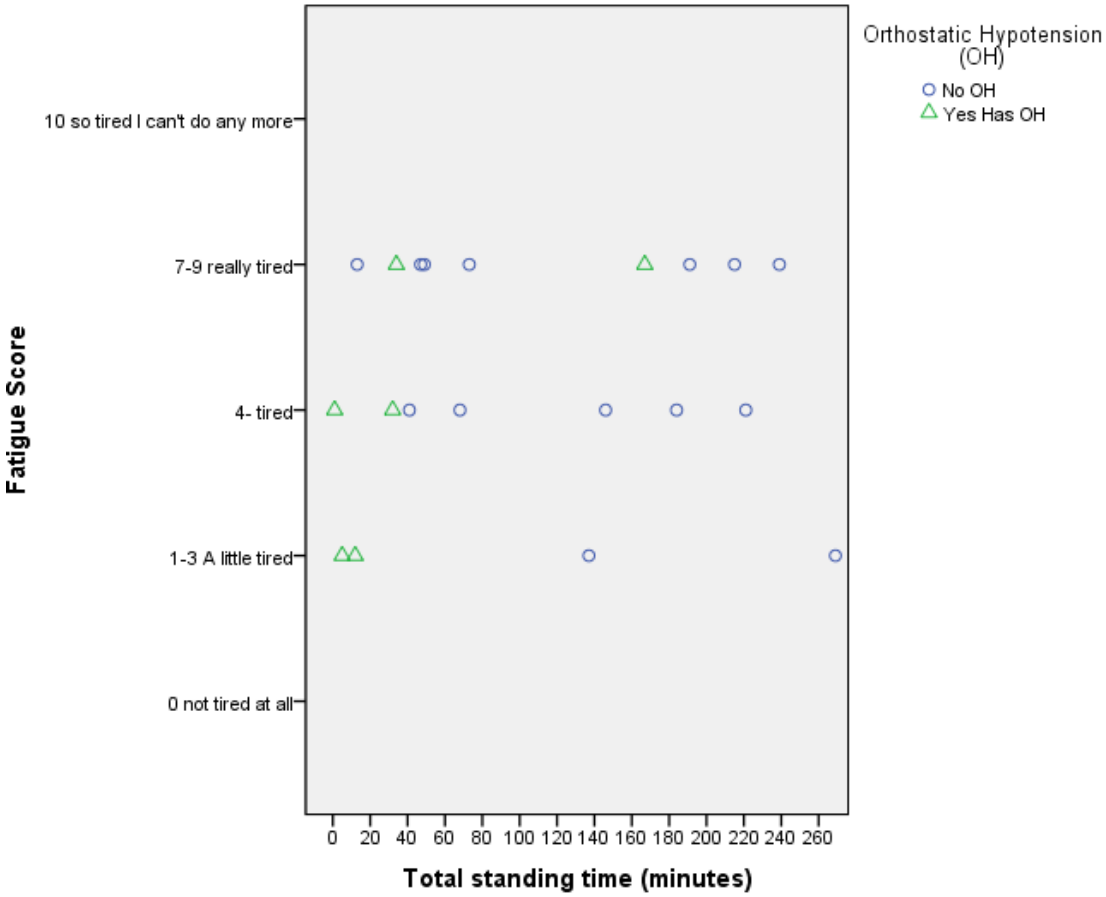


Figure 4.18 Relationship between adherence of standing time, orthostatic hypotension and fatigue measured during intervention sessions

There was no significant relationship between OH and fatigue in participants in the intervention group, as shown by the Chi-Square test in Table 4.6.

	Fatigue 0-3	Fatigue 4-6	Marginal Row Totals
Has OH	3	3	6
Does not have OH	9	7	16
Marginal Column Totals	12	10	22 (Grand total)

The Fisher exact test statistic value is 1. The result is not significant at $p < .05$

Table 4.6 Chi square test for orthostatic hypotension and fatigue in the intervention group

It was anticipated that OH may affect participants' ability to complete some intervention sessions (see Chapter 2). Orthostatic hypotension occurred in 21 out of 426 sessions (Table 4.7). Nine participants experienced OH: three in the control group and six in the intervention group. The prevalence of OH is slightly higher in the intervention group (n=6) than is reported in the minimisation procedure data (n=4). This may likely be because the assessment for OH during the minimisation procedure is lying to upright sitting, whereas participants in the intervention group were moving from sitting to standing. Orthostatic hypotension affected completion of 13 sessions (7.2%) in the intervention group and 0.8% (n=2) in the control group. Participants required treatment for OH during 12 sessions (6.7%); six of which entailed pharmacological treatment.

Parameter	**Intervention group % within allocation (n)** [n=180 sessions]	**Control group % within allocation (n)** [n=246 sessions]
Number of sessions OH occurred	8.3 (15)	2.4 (6)
Number of times OH needed treatment	6.7 (12)	0.0 (0)
Treatment pharmacological	3.3 (6*)	0.0 (0)
Treatment non-pharmacological	2.8 (5*)	0.0 (0)
Number of times OH affected completion of the session	7.2 (13)	0.8 (2)

*Spoiled CRF; OH, orthostatic hypotension

Table 4.7 Prevalence, impact and treatment of orthostatic hypotension

4.8 Content of usual physiotherapy across both groups

Supported standing, supported sitting and unsupported sitting were the most commonly adopted postures during the control group rehabilitation sessions and during the 15 minutes of usual physiotherapy as part of the intervention (Table 4.8). Based on percentages, the groups were similar except supine was

more commonly used in treatment activities in the control group. Supported standing was the most commonly adopted position in the control group and used in 161 (63.63%) of sessions. Two sites used supported standing most frequently in the control group: site 1 n=59 sessions, site 3 n=85 sessions. Twenty-one participants (over 161 sessions) in the control group performed supported standing, ranging from one to 14 sessions per participant. However, the number of minutes participants spent in supported standing and equipment used were not captured in the CRFs. Additionally, there did not appear to be any pattern to this, e.g., practice changing over time throughout the trial.

Participants' positions during usual physiotherapy (number of sessions the positions were used out of 429 completed sessions, not per participant and not mutually exclusive)	**Intervention group during usual physio component % (n)** [n=176 sessions]	**Control % (n)** [n=253 sessions]
Supine	16.50 (29)	37.94 (96)
Prone	0.00 (0)	0.00 (0)
Side lying (affected side)	1.70 (3)	9.50 (24)
Side lying (unaffected side)	2.84 (5)	8.30 (21)
Supported sitting	51.13 (90)	50.20 (127)
Supported standing	54.54 (96)	63.63 (161)
Perch sitting	5.11 (9)	9.10 (23)
Unsupported sitting	54.54 (96)	41.10 (104)
Unsupported standing	9.10 (16)	6.77 (17)
Prone standing	0.00 (0)	0.00 (0)
4-point kneeling	0.00 (0)	0.00 (0)
2-poing kneeling	0.00 (0)	0.00 (0)
Crook lying	1.70 (3)	7.51 (19)

Table 4.8 Gross position of participants during usual physiotherapy for both groups

A total of 429 usual physiotherapy sessions were completed: n=253 in the control group and n=176 in the intervention group. More participants withdrew from the intervention group, contributing to the higher number of sessions completed in the control group. Treatment activities varied between groups

(Table 4.9), specifically in exercises to improve strength, upper limb tasks, facilitation of movement, sensory stimulation and functional tasks.

Exercises to improve strength were low in both groups but used in more sessions in the intervention group. This may be due to standing and sit to stand repetitions being considered as strengthening exercises, thus double counted. Functional activities were high in the control group, but this included washing and dressing as well as sit to stand, therefore, the tasks specifically undertaken in this category are unknown.

Treatments activities undertaken by participants during usual physiotherapy [number of sessions treatment activities were used out of 429 completed sessions, not per participant and not mutually exclusive]	**Intervention group during 15 minutes usual physiotherapy component % (n)** [n=176 sessions]	**Control % (n)** [n=253 sessions]
Exercise to improve cardiovascular fitness	2.84 (5)	3.47 (9)
Exercise to improve strength	22.72 (40)	4.74 (12)
Exercise to improve co-ordination	1.13 (2)	5.92 (15)
Upper limb tasks	21.60 (38)	30.83 (78)
Facilitation of movement/muscle activation	26.13 (46)	40.71 (103)
Soft tissue mobilisation	1.13 (2)	2.80 (7)
Joint mobilisation	7.40 (13)	9.10 (23)
Sensory stimulation	8.00 (14)	19.40 (49)
Balance activities (static)	21.60 (38)	27.70 (70)
Balance activities (dynamic)	13.10 (23)	25.30 (64)
Functional tasks (e.g. sit to stand, wash/dress)	22.72 (40)	53.80 (136)
Practising transfers	48.90 (86)	49.01 (124)
Stepping/walking/gait re-education	23.90 (42)	19.40 (49)
Review/progress seating	5.70 (10)	9.10 (23)
Positioning	15.34 (27)	20.20 (51)
Tone management	6.25 (11)	10.70 (27)
Oedema management	2.30 (4)	1.19 (3)
Pain management	1.13 (2)	1.60 (4)
Splinting	0.00	2.00 (5)
Orthotics	1.13 (2)	0.00
Education/training for patient and/or family/carers	1.13 (2)	2.40 (6)

Other treatment activities		
Acupuncture	0.00 (0)	0.00 (0)
Taping (e.g. ROCK or kinesiology tape)	7.95 (14)	3.20 (8)
Ultrasound	0.00 (0)	0.00 (0)
Compression	0.00 (0)	0.40 (1)
Warm water bathing	0.00 (0)	0.00 (0)
Body weight support treadmill training	0.00 (0)	0.00 (0)
Functional electrical stimulation	1.13 (2)	4.34 (11)
Microstim	0.00 (0)	0.00 (0)
Hydrotherapy	0.00 (0)	0.00 (0)
Theraband	0.00 (0)	0.00 (0)
Nintendo Wii or other virtual reality games	0.00 (0)	0.00 (0)
Lycra/compression garments	0.00 (0)	0.00 (0)
Other*	8.52 (15)	18.60 (47)

*motoMED (cycle ergometer), respiratory physiotherapy, neck exercises, cognitive assessment with Occupational Therapist

Table 4.9 Treatment activities undertaken by participants during usual physiotherapy for both groups

4.9 Experience of the intervention

Brief interviews were conducted at the end of 167 intervention sessions. Brief interviews were not conducted or completed for n=9 sessions (n=5 participants). Reasons were not captured but all five participants had aphasia and/or cognitive impairment. Table 4.10 shows that most sessions (91.0%) were reported to being enjoyed by participants. Most sessions required moderate (46.1%) or severe (32.3%) effort, and at the end of 33.5% sessions participants were tired, 31.7% really tired and 22.8% a little tired. Participants did not report experiencing aches or pains in most sessions (66.5%).

Enjoyment of each completed session %	**Yes (enjoyed)**	**No (did not enjoy)**
	91.0 (152)	9.0 (15)
Effort	**% (n) per completed session**	
None (0)	1.2 (2)	
Mild (1-3)	12.6 (21)	
Moderate (4-6)	46.1 (77)	
Severe (7-9)	32.3 (54)	
Unbearable (10)	0.0 (0)	
Missing	7.8 (13)	

Fatigue	**% (n) per completed session**
Not at all (0)	3.0 (5)
A little tired (1-3)	22.8 (38)
Tired (4-6)	33.5 (56)
Really tired (7-9)	31.7 (53)
So tired I can't do anything (10)	5.4 (9)
Missing	3.6 (6)
Aches and pains	**% (n) per completed session**
None (0)	66.5 (111)
Mild (1-3)	10.2 (17)
Moderate (4-6)	9.6 (16)
Severe (7-9)	9.6 (16)
Worst pain possible (10)	0.6 (1)
Missing	3.6 (6)

Table 4.10 Experience of the intervention (enjoyment, effort, fatigue, aches and pains)

The work instruction stipulated brief interviews were conducted at the end of the intervention session. Therefore, it is not known whether responses to the assessed domains in Table 4.10 were related specifically to the standing frame or the whole session which included 15 minutes usual physiotherapy activities.

Participants reported fatigue for 93.4% (n=156) of sessions that the brief interviews were conducted. Figure 4.19 shows that their fatigue fluctuated over the 21 sessions and participants did not appear to be experiencing more fatigue at the start of the 21 days, e.g. soon after their stroke, or at the end of the trial.

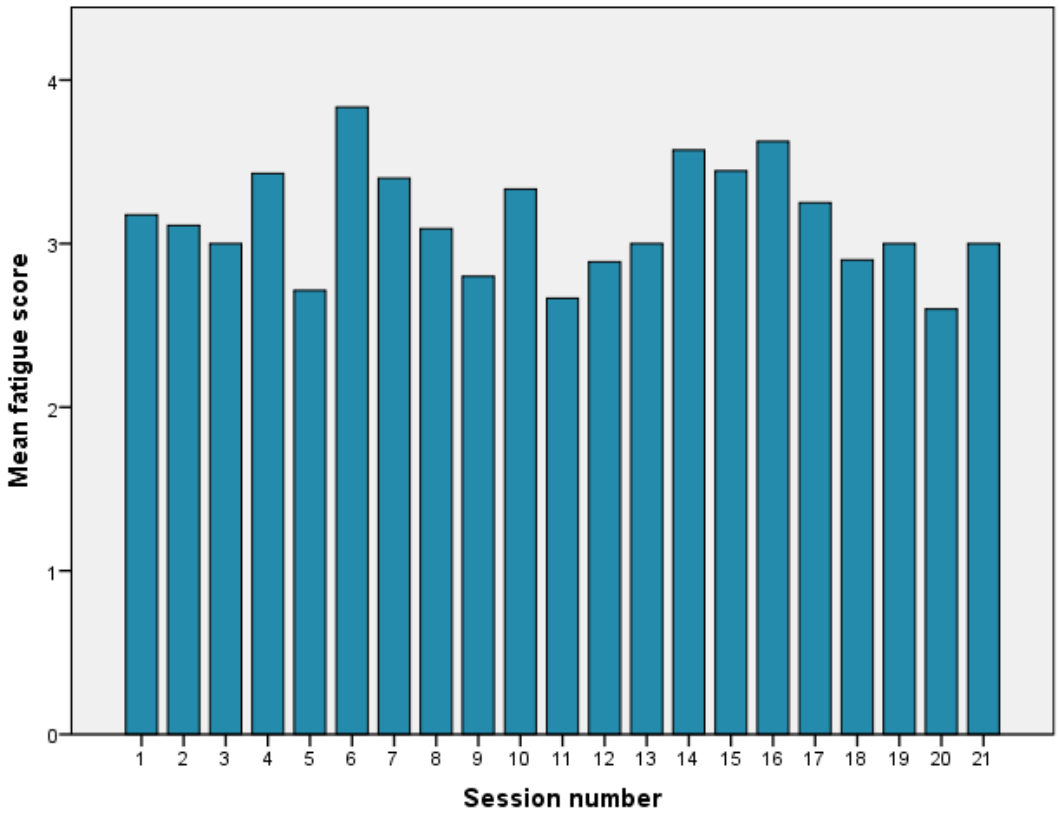


Figure 4.19 Fatigue scores over the 3-week trial period

4.10 Adverse and serious adverse events

4.10.1 Adverse events

A total of 118 AEs were reported during the whole trial (3-week treatment and follow-up period): 59 in each group (Table 4.11). Thirty-eight participants had AEs: 20 in the intervention group and 18 in the control group. During the 3-week treatment period 10 AEs were reported in the control group and 16 in the intervention group. The most common AEs were falls, respiratory, thoracic and mediastinal disorders and renal disorders, all slightly higher in the control group.

Proportion of AEs: six participants had one, 12 had two, seven had three, five had four, three had five, four had six and one had eight. Therefore, the count of participants with AEs and percentage in the right column of each group in Table 4.11 is not equal to the number of participants allocated to each group. AEs were similar in both groups.

Organ system	Intervention		Control	
	Count (n) and % of AEs within allocation* n=22	Count (n) and % of participants with AEs** n=45	Count and % of AEs within allocation* n=23	Count and % of participants with AEs** n=45
Blood and the lymphatic system disorders	13.6 (3)	4.44 (2)	4.34 (1)	2.22 (1)
Cardiac disorders	9.10 (2)	4.44 (2)	0.00 (0)	0.00 (0)
Congenital and familial and genetic disorders	0.00 (0)	0.00 (0)	4.34 (1)	2.22 (1)
Ear and labyrinth disorders	0.00 (0)	0.00 (0)	4.34 (1)	2.22 (1)
Endocrine system	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
End of life care	4.54 (1)	2.22 (1)	0.00 (0)	0.00 (0)
Fall	68.18 (15)	15.56 (7)	82.6 (19)	20.00 (9)
Gastrointestinal disorders	18.18 (4)	6.67 (3)	8.70 (2)	4.44 (2)
General disorders and admin site conditions	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Hepatobiliary disorders	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Infections and infestations	22.73 (5)	8.89 (4)	26.10 (6)	11.11 (5)
Injury, poisoning and procedural complications	4.54 (1)	2.22 (1)	4.34 (1)	2.22 (1)
Metabolism and nutrition disorders	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Musculoskeletal and connective tissue disorders	4.54 (1)	2.22 (1)	4.32 (1)	2.22 (1)
Nervous system disorders	18.18 (4)	8.9 (4)	13.04 (3)	4.44 (2)
Orthostatic hypotension	18.18 (4)	6.67 (3)	0.00 (0)	0.00 (0)
Psychiatric disorders	4.54 (1)	2.22 (1)	0.00 (0)	0.00 (0)
Renal and urinary disorders	27.27 (6)	11.11 (5)	30.43 (7)	8.89 (4)
Respiratory, thoracic and mediastinal disorders	40.91 (9)	13.33 (6)	60.90 (14)	13.33 (6)
Skin and subcutaneous tissue disorders	9.10 (2)	4.44 (2)	13.04 (3)	6.67 (3)
Surgical and medical procedures	4.54 (1)	22.22 (1)	0.00 (0)	0.00 (0)
Total (n)	**59 AEs**	**20* participants**	**59 AEs**	**18* participants**

Most participants had more than one AE reported in the same or different organ system therefore this number does not equal the total number in this column

*Calculated by number of AEs divided by total number of participants in this group

**Calculated by number of people with AEs divided by total number of participants

Table 4.11 Adverse events in both groups

4.10.2 Serious adverse events

Twenty AEs listed in Table 4.10 above were classified as serious and 10 additional serious adverse events (SAEs) were reported separately, thus a total of 30 SAEs (Table 4.12) were reported during the trial: 17 in the intervention group and 13 in the control group. Twenty-five participants had SAEs: 12 in the intervention group and 13 in the control group. During the 3-week treatment period two SAEs were recorded for two participants, both in the intervention group. The remaining n=28 were recorded during the follow-up period. SAEs were similar in both groups. The most common SAEs were infections (slightly higher in the intervention group). Proportion of SAEs: n=15 participants had one, n=6 had two and n=1 had three.

Organ system	Intervention		Control	
	Count (n) and % of SAEs within allocation* n=22	Count (n) and % of participants with SAEs** n=45]	Count and % of SAEs within allocation* n=23	Count and % of participants with SAEs** n=45
Blood and the lymphatic system disorders	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Cardiac disorders	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Congenital and familial and genetic disorders	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Ear and labyrinth disorders	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Endocrine system	0.00 (0)	0.00 (0)	4.34 (1)	2.22 (1)
End of life care	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Fall	4.54 (1)	2.22 (1)	0.00 (0)	0.00 (0)
Gastrointestinal disorders	9.09 (2)	4.44 (2)	0.00 (0)	0.00 (0)
General disorders and admin site conditions	4.54 (1)	2.22 (1)	4.34 (1)	2.22 (1)
Hepatobiliary disorders	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Infections and infestations	31.82 (7)	11.11 (5)	21.7 (5)	11.11 (5)
Injury, poisoning and procedural complications	9.09 (2)	4.44 (2)	8.70 (2)	4.44 (2)
Metabolism and nutrition disorders	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Musculoskeletal and connective tissue disorders	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)

Nervous system disorders	9.09 (2)	4.44 (2)	8.70 (2)	6.67 (3)
Orthostatic hypotension	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Psychiatric disorders	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Renal and urinary disorders	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Respiratory, thoracic and mediastinal disorders	4.54 (1)	2.22 (1)	4.34 (1)	2.22 (1)
Skin and subcutaneous tissue disorders	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Surgical and medical procedures	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Unknown	4.54 (1)	2.22 (1)	0.00 (0)	0.00 (0)
Total (n)	**17 AEs**	**12† participants**	**13 AEs**	**13† participants**

†Seven participants had more than one SAE reported in the same or different organ system therefore this number does not equal the total number in this column

*Calculated by number of AEs divided by total number of participants in this group **Calculated by number of people with AEs divided by total number of participants

Table 4.12 Serious adverse events in both groups

Table 4.13 presents the AEs and SAEs by site. Site 1 had the highest number of AEs, which was unsurprising given they recruited the highest number of participants. Sites 1 and 3 had the highest number of SAEs and when reviewing the proportion of participants recruited to the number of SAEs, site 3 had the highest number of SAEs.

	Site 1 % (n of AE or SAE)		**Site 2 % (n of AE or SAE)**		**Site 3 % (n of AE or SAE)**		**Site 4 % (n of AE or SAE)**	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
AE % within site total	39.0 (46)	21.2 (25)	1.7 (2)	5.9 (7)	6.8 (8)	22.9 (27)	2.5 (3)	0.0 (0)
AE total % across 4 sites	60.2 (71)		7.6 (9)		29.7 (35)		2.5 (3)	
SAE% within site total	33.3 (10)	10.0 (3)	0.0 (0)	10.0 (3)	13.3 (4)	23.3 (7)	(3)	0.0 (0)
SAE total % across four sites	43.3 (13)		10.0 (3)		36.6 (11)		10.0 (3)	

Table 4.13 Adverse Events and Serious Adverse Events by site

Twelve participants (26.7%) died during the trial, seven (15.6%) in the intervention group and five (11.1%) in the control group (Table 4.14). Two participants (4.4%) in the intervention group died during the 3-week treatment period and five (11.1%) died in the follow-up period compared to five participants (11.1%) in the control group who all died during the follow-up period. The highest number of deaths occurred between 29 and 55 weeks. Details of which time-points deaths occurred are shown in Figure 4.1 (CONSORT).

Organ system	Deaths in group allocation % (n)	
	Intervention	Control
Infections and infestations	0.0 (0)	4.3 (1)
Nervous system disorders	0.0 (0)	8.7 (2)
Respiratory, thoracic and mediastinal disorders	0.0 (0)	4.3 (1)
General disorders and administration site conditions	0.0 (0)	4.3 (1)
Infections and infestations	18.2 (4)	0.0 (0)
Nervous system disorders	4.5 (1)	0.0 (0)
General disorders and administration site conditions	4.5 (1)	0.0 (0)
Unknown	4.5 (1)	0.0 (0)

Table 4.14 Total number and causes of death in both groups

Eleven of the 12 participants who died were aged ≥80 years: n=8 in their 80s, n=3 in their 90s. One participant was 72 years of age. Eight of the participants (66.7%) who died were from site 1. Deaths at other sites were: one (8.3%) from site 2, two (16.7%) from site 3 and one (8.3%) from site 4.

4.10.3 Relationship of adverse and serious adverse events and stroke severity

The relationship between AEs and SAEs are shown in Tables 4.15a and 4.15b. Most AEs were recorded in participants with moderately severe stroke (mRS 4) (86.4% in the intervention group and 91.5% in the control group) (Table 4.15a).

There were slightly more AEs in the intervention group (13.6%) compared to the control group (8.5%) for participants with very severe stroke (mRS 5).

Relatedness of AEs was not recorded.

Stroke severity	Adverse Events % (n)		Total number (n) of AEs
	Intervention Group	Control group	
Moderately severe stroke (mRS 4)	86.4 (51)	91.5 (54)	(105)
Very severe stroke (mRS 5)	13.6 (8)	8.5 (5)	(13)

Table 4.15a Relationships between Adverse Event and stroke severity in both groups

Table 4.15b shows the relationship between SAEs and stroke severity and relatedness of SAEs to the trial. In total there were 30 SAEs, (n=17 (56.7%) in the intervention group and n=13 (43.3%) in the control group and) none which were considered related to the trial.

Stroke severity	SAEs	
	Intervention % (n) within group	Control % (n) within group
mRS 4 Unlikely	23.52 (4)	38.50 (5)
mRS 4 Not related	52.94 (9)	38.50 (5)
mRS 5 Unlikely	0.00 (0)	0.00 (0)
mRS 5 Not related	23.52 (4)	23.10 (3)

Table 4.15b Relationships between Serious Adverse Events (SAEs) and stroke severity and relatedness of SAEs to the trial in both groups

4.11 Outcomes

4.11.1 Primary outcome measures

The BI has a maximum score of 20, and the Edmans has maximum subgroup scores of 9. In both measures a lower score indicates increased dependency/disability. BI scores increased over time (Table 4.16a). For both

groups, initially this was more marked between baseline to 3 weeks, then a slower increase between 3-29 weeks, before it plateaued between 29-55 weeks for the intervention group, and a slight decrease for the control group. Scores varied for the Edmans subgroups, with mean scores in washing, meal times, bed mobility and advanced mobility scores increasing at each time point in the intervention group, but scores in all subgroups improved from baseline to 55 weeks in both groups. Both measures were able to detect change in people with severe stroke, but the Edmans shows changes in scores in individual subgroups. This will be expanded upon in Section 4.15 (Responsiveness of proposed outcome measures).

Outcome variable	Treatment Group	Baseline	Time point 3 (+/-1) weeks	15 weeks (+/-1 week)	29 weeks (+/-1 week)	55 weeks (+/-1 week)
Barthel Index total						
Mean (SD) [range]	*Intervention*	2.32 (2.056) [0-8]	5.53 (5.293) [1-20]	7.0 (6.066) [0-20]	7.88 (6.888) [1-20]	8.33 (7.762) [1-20]
	Control	2.57 (2.573) [0-10]	5.05 (4.675) [0-16]	6.82 (5.992) [1-19]	7.69 (6.085) [1-19]	7.47 (6.446) [0-16]
Median (IQR)	*Intervention*	1.50 (3)	2.00 (7)	5.50 (9)	4.00 (12)	4.50 (16)
	Control	1.00 (4)	3.0 (8)	3.0 [10]	6.50 (12)	7.00 (14)
Edmans Activities of Daily Living Index for Stroke subgroup totals Mean (SD) [range]						
Washing Mean (SD) [range]	*Intervention*	0.73 (0.50) [0-2]	2.18 (6.40) [0-9]	2.63 (2.90) [0-9]	2.63 (3.40) [0-9]	3.25 (3.77) [0-9]
	Control	0.57 (0.66) [0-2]	1.77 (2.12) [0-9]	2.235 (2.26) [0-9]	2.63 (2.39) [0-7]	2.33 (2.29) [0-7]
Grooming Mean (SD) [range]	*Intervention*	2.18 (2.99) [0-9]	4.41 (2.81) [0-9]	5.00 (3.16) [0-9]	4.50 (3.78) [0-9]	4.83 (3.81) [0-9]
	Control	2.57 (3.10) [0-9]	4.23 (3.68) [0-9]	5.06 (3.78) [0-9]	5.63 (3.14) [0-9]	4.93 (3.69) [0-9]
Dressing Mean (SD) [range]	*Intervention*	0.32 (0.72) [0-3]	1.82 (2.74) [0-9]	1.81 (3.02) [0-9]	2.13 (3.50) [0-9]	3.08 (4.03) [0-9]
	Control	0.39 (0.72) [0-3]	1.45 (2.32) [0-9]	2.00 (2.83) [0-9]	2.13 (2.96) [0-9]	2.47 (3.34) [0-9]
Meal times Mean (SD) [range]	*Intervention*	2.91 (3.01) [0-9]	5.06 (3.09) [0-9]	6.06 (2.91) [0-9]	6.38 (3.05) [0-9]	6.83 2.41) [2-7]
	Control	3.35 (3.28) [0-9]	5.14 (3.90) [0-9]	6.94 (2.66) [0-9]	6.44 (2.99) [0-9]	6.53 (3.18) [0-9]
Basic mobility	*Intervention*	0.73 (0.76)	2.59 (2.76)	3.19 (2.97)	3.94 (3.77)	3.92 (3.83)

Mean (SD) [range]		[0-2]	[0-9]	[0-9]	[0-9]	[0-9]
	Control	0.74 (1.05) [0-4]	2.05 (2.48) [0-9]	3.18 (3.59) [0-9]	3.50 (3.78) [0-9]	4.13 (4.22) [0-9]
Advanced mobility Mean (SD) [range]	*Intervention*	0.04 (0.21) [0-1]	1.18 (2.35) [0-9]	1.56 (3.05) [0-9]	2.13 (3.34) [0-9]	2.25 (3.49) [0-9]
	Control	0.04 (0.21) [0-1]	0.32 (1.09) [0-5]	1.24 (1.86) [0-5]	1.69 (2.70) [0-9]	1.80 (2.43) [0-7]
Bed mobility Mean (SD) [range]	*Intervention*	0.14 (0.64) [0-3]	2.06 (2.73) [0-9]	2.25 (3.32) [0-9]	3.25 (4.07) [0-9]	3.50 (4.17) [0-9]
	Control	0.22 (0.74) [0-3]	1.68 (2.46) [0-9]	2.47 (3.30) [0-9]	3.00 (3.86) [0-9]	3.93 (4.37) [0-9]
Kitchen activities Mean (SD) [range]	*Intervention*	0.05 (0.21) [0-1]	0.65 (1.97) [0-8]	1.38 (3.07) [0-9]	1.69 (3.24) [0-9]	1.17 (2.73) [0-9]
	Control	0.05 (0.21) [0-1]	0.73 (1.67) [0-6]	1.59 (2.87) [0-9]	1.50 (2.53) [0-7]	1.27 (2.25) [0-7]
Housework activities Mean (SD) [range]	*Intervention*	0.00 (0) [0]	0.41 (1.70) [0-7]	1.13 (3.07) [0-9]	1.06 (2.91) [0-9]	0.92 (2.61) [0-9]
	Control	0.00 (0) [0]	0.09 (0.43) [0-2]	0.18 (0.73) [0-3]	0.31 (0.87) [0-3]	0.33 (1.05) [0-4]
Washing Median [IQR]	*Intervention*	1.00 [1]	1.00 [4]	1.00 [3]	1.00 [4]	1.50 [8]
	Control	0.00 [1]	1.00 [3]	2.00 [3]	1.50 [4]	1.00 [4]
Grooming Median [IQR]	*Intervention*	0.00 [4]	4.00 [4]	5.00 [6]	4.00 [9]	5.00 [9]
	Control	1.00 [4]	3.50 [8]	4.00 [8]	6.00 [6]	5.00 [9]
Dressing Median [IQR]	*Intervention*	0.00 [0]	0.00 [3]	0.50 [2]	0.00 [2]	1.00 [8]
	Control	0.00 [1]	0.00 [2]	0.00 [3]	0.50 [5]	0.00 [6]

Meal times Median [IQR]	*Intervention*	2.5 [5]	6.00 [6]	6.50 [6]	6.50 [4]	7.00 [5]
	Control	3.00 [6]	6.50 [9]	7.00 [3]	7.00 [5]	7.00 [2]
Basic mobility Median [IQR]	*Intervention*	1.00 [1]	1.00 [5]	2.00 [5]	3.00 [9]	3.00 [9]
	Control	0.00 [1]	1.50 [4]	1.00 [6]	2.00 [8]	3.00 [9]
Advanced mobility Median [IQR]	*Intervention*	0.00 [0]	0.00 [0]	0.00 [2]	0.00 [5]	0.00 [4]
	Control	0.00 [0]	0.00 [2]	0.00 [3]	0.00 [4]	0.00 [4]
Bed mobility Median [IQR]	*Intervention*	0.00 [0]	1.00 [4]	0.00 [5]	1.00 [9]	1.50 [9]
	Control	0.00 [0]	0.50 [3]	0.00 [5]	0.50 [8]	2.00 [9]
Kitchen activities Median [IQR]	*Intervention*	0.00 [0]	0.00 [0]	0.00 [1]	0.00 [1]	0.00 [1]
	Control	0.00 [0]	0.00 [0]	0.00 [3]	0.00 [3]	0.00 [2]
Housework activities Median [IQR]	*Intervention*	0.00 [0]	0.00 [0]	0.00 [0]	0.00 [0]	0.00 [0]
	Control	0.00 [0]	0.00 [0]	0.00 [(0]	0.00 [0]	0.00 [0]

Table 4.16a Proposed primary outcome data

The Edmans has included “Associated Problems” as a measurement category which is scored out of 10, with a higher score representing increased number of problems. Participants in the intervention group had a higher prevalence of sensory, perceptual, dyspraxia, reasoning, memory, urinary continence problems and made the greatest improvements in all these domains except perceptual problems (Table 4.16b). Although scores fluctuated at 3, 15 and 29 weeks, the scores decreased (indicating reduced prevalence) from baseline in both groups in language, perceptual, sensory, dyspraxia, reasoning, anxiety and continence problems. Memory problems increased in the control group and depression problems scores increased in both groups.

Associated problems	Treatment group	Time point: Baseline (n=45)	3 (+/-1) weeks (n=39)	15 weeks (+/-1 week) (n=33)	29 weeks (+/-1 week) (n=32)	55 weeks (+/-1 week) (n=27)
Language problems	*Intervention*	68.2 (11)	52.9 (9)	62.5 (10)	62.5 (10)	41.7 (5)
	Control	47.8 (15)	50.0 (11)	35.3 (6)	31.3 (5)	33.3 (5)
Perceptual problems	*Intervention*	68.2 (15)	41.2 (7)	31.3 (5)	37.5 (6)	25.0 (3)
	Control	56.5 (13)	27.3 (6)	23.5 (4)	25.0 (4)	13.3 (2)
Sensory problems	*Intervention*	100.0 (22)	82.4 (14)	75.0 (12)	87.5 (14)	75.0 (9)
	Control	82.6 (19)	72.7 (16)	82.4 (14)	68.8 (11)	93.3 (14)
Dyspraxia problems	*Intervention*	27.3 (6)	23.5 (4)	6.3 (1)	12.5 (2)	8.3 (1)
	Control	13.0 (3)	9.1 (2)	0.00 (0)	0.00 (0)	0.00 (0)
Reasoning problems	*Intervention*	77.3 (17)	76.5 (13)	56.3 (9)	75.0 (12)	41.7 (5)
	Control	65.2 (15)	59.1 (13)	58.8 (10)	50.0 (8)	53.3 (8)
Memory problems	*Intervention*	81.1 (18)	94.1 (16)	81.3 (13)	93.8 (15)	75.0 (9)
	Control	73.9 (17)	90.0 (20)	94.1 (16)	93.8 (15)	93.3 (14)
Depression problems	*Intervention*	36.4 (8)	35.3 (6)	75.0 (12)	56.3 (9)	66.7 (8)
	Control	47.8 (11)	18.2 (4)	41.2 (7)	62.5 (10)	46.7 (7)
Anxiety problems	*Intervention*	31.8 (7)	23.5 (4)	43.8 (7)	43.8 (7)	25.0 (3)
	Control	47.8 (11)	45.5 (10)	47.1 (8)	37.5 (6)	33.3 (5)
Urinary continence problems	*Intervention*	90.9 (20)	88.2 (15)	68.8 (11)	81.3 (13)	58.3 (7)
	Control	87.0 (20)	72.7 (16)	70.6 (12)	62.5 (10)	80.0 (12)
Faecal continence problems	*Intervention*	87.0 (20)	88.2 (15)	56.3 (9)	68.8 (11)	58.3 (7)
	Control	90.9 (20)	63.6 (14)	76.5 (13)	62.5 (10)	66.7 (10)

Table 4.16b Proposed primary outcome data (Associated Problems for the Edmans ADL Index for Stroke Patients)

4.11.2 Ability to self-report proposed primary outcome measures

Cognitive and/or communication impairment affected some participants' ability to complete the patient report outcome measure, therefore a proxy was used (clinician, relative or carer). The proportion of patient and proxy responses for the proposed primary outcome measures are shown in Figure 4.20. Ability to self-report was the same for both primary outcome measures, which was similar at all time- points: 19 participants (42.2%) at baseline and 22 (48.9%) at 55 weeks.

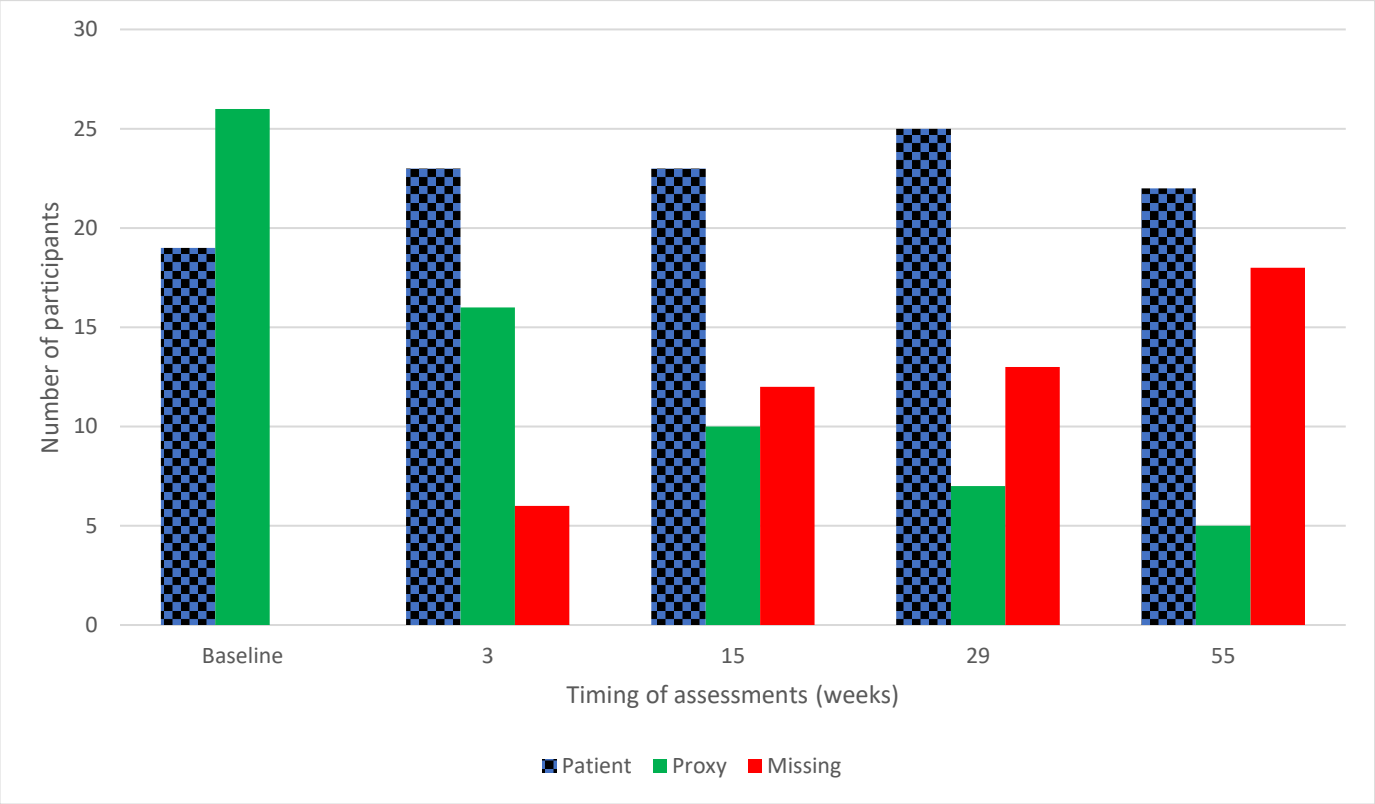


Figure 4.20 Proportion of participant versus proxy responses for both proposed primary outcome measures

4.11.3 Secondary outcome measures

The secondary outcome measures are a combination of physical measures taken by the blinded assessor and patient report outcome measures administered by the blinded assessor (Table 4.17a and 4.17b). Fewer participants completed the patient report outcome measures than the physical measures, due to cognitive and/or communication impairment. One participant in the control group declined most of the muscle length, strength and tone testing on his hemi-paretic lower limb at baseline because of hypersensitivity, pain and anxiety, and then all physical measures at 15, 29 and 55 weeks. This participant completed all proposed primary and patient-reported outcome measures at all time-points. One participant in the intervention group declined all outcome measures except the Trunk Control Test at 55-week visit. One participant missed their 3-week visit due to being medically unwell but had their 15-week visit, then died prior to their 29-week visit.

Hip flexor length varied in both groups for each of the time points. Hip flexor length reduced over time, most notably from 15 weeks to 29 weeks in the intervention group, and participants' right hip in the intervention group had the biggest loss of muscle length (4.5 degrees from baseline to 55 weeks). Hamstring length reduced over time in both groups. Participants in the intervention group had less range of movement than the control group at baseline. Dorsiflexor length varied between groups. The change from baseline to three weeks varied from -0.50 to -2.50 degrees, and a median loss of -3.00 degrees seen at 15 and 29 weeks. Ankle plantar flexor length was similar in both groups across the different time points. In summary, the changes seen are generally small, which did not exceed the five or 10 degrees minimally clinically important difference proposed by Katalinic et al[350] for range of motion.

Outcome variable	Time point	LEFT		RIGHT	
		Intervention Group median [IQR] (n)	**Control Group** median [IQR] (n)	**Intervention Group** median [IQR] (n)	**Control Group** median [IQR] (n)
Muscle length using manual goniometry Hip extension (Hip angle)	Baseline	-1.50 [4] (22)	-1.0 [10] (22)	-0.50 [6] (22),	0.00 [5] (22)
	3 weeks	-1.00 [3] (17)	0.00 [5] (21)	-2.00 [6] (17)	0.00 [2] (20)
	15 weeks	0.00 [11] (15)	0.00 [4] (16)	0.00 [8] (15)	0.00 [5] (16)
	29 weeks	1.50 [14] (16)	2.00 [6] (15)	1.50 [15] (16)	0.00 [9] (15)
	55 weeks	0.00 [10] (11)	1.50 [9] (14)	4.00 [12] (11)	1.00 [10] (14)
Knee extension (popliteal angle)	Baseline	38.50 [13] (22)	31.00 [14] (22)	37.50 [8] (22)	32.00 [15] (23)
	3 weeks	38.00 [13] (17)	38.00 [14] (21)	35.00 [12] (17)	36.00 [12] (21)
	15 weeks	40.00 [18] (16)	38.50 [8] (16)	41.00 [18] (16)	39.50 [10] (16)
	29 weeks	40.00 [15] (16)	45.00 [11] (15)	43.50 [16] (16)	42.00 [13] (15)
	55 weeks	42.00 [18] (11)	44.00 [12] (14)	47.00 [7] (11)	42.00 [16] (14)
Ankle dorsiflexion	Baseline	-0.50 [5] (22)	-1.00 [8] (22)	-2.50 [7] (22)	-2.00 [6] (23)
	3 weeks	0.00 [3] (17)	-2.00 [5] (21)	-2.00 [3] (17)	-2.00 [4] (21)
	15 weeks	-1.00 [6] (16)	-2.00 [7] (17)	0.00 [12] (16)	-3.00 [7] (17)
	29 weeks	-3.00 [8] (16)	-2.00 [11] (15)	0.00 [10] (16)	0.00 [11] (15)
	55 weeks	-2.00 [9] (11)	-0.50 [21] (14)	0.00 [18] (11)	-0.50 [17] (14)
Ankle plantarflexion	Baseline	37.50 [9] (22)	39.50 [18] (22)	37.00 [10] (22)	39.00 [14] (23)
	3 weeks	43.00 [10] (17)	42.00 [9] (21)	40.00 [15] (17)	42.00 [12] (21)
	15 weeks	42.00 [11] (16)	38.00 [16] (17)	41.00 [3] (15)	36.00 [16] (17)
	29 weeks	42.00 [7] (16)	39.00 [6] (15)	42.00 [6] (16)	39.00 [10] (15)
	55 weeks	40.00 [16] (11)	40.00 [15] (14)	39.00 [12] (11)	37.00 [14] (14)
Knee extensor muscle strength measured in Newtons (Maximum score of three trials)	Baseline	58.00 [29] (22)	54.00 [48] (22)	40.50 [49] (22)	62.00 [47] (22)
	3 weeks	69.00 [33] (17)	69.00 [59] (21)	60.00 [31] (17)	60.00 [39] (21)
	15 weeks	57.00 [44] (15)	56.50 [40] (16)	57.00 [86] (15)	64.00 [26] (16)
	29 weeks	70.00 [37] (16)	57.00 [37] (15)	57.00 [45] (16)	69.00 [36] (15)
	55 weeks	67.00 [55] (11)	58.00 [56] (14)	73.00 [89] (11)	76.00 [38] (14)
Modified Ashworth scale					

Hip adductors	Baseline	0.00 [0] (22)	0.00 [0] (22)	0.00 [0] (22)	0.00 [0] (23)
	3 weeks	0.00 [0] (17)	0.00 [0] (21)	0.00 [0] (17)	0.00 [0] (21)
	15 weeks	0.00 [0] (16)	0.00 [1] (16)	0.00 [0] (16)	0.00 [0] (17)
	29 weeks	0.00 [1] (16)	0.00 [1] (15)	0.00 [1] (16)	0.00 [1] (15)
	55 weeks	0.00 [1] (11)	0.00 [1] (14)	0.00 [0] (11)	0.00 [1] (14)
Hamstrings	Baseline	0.00 [0] (22)	0.00 [0] (22)	0.00 [0] (22)	0.00 [0] (23)
	3 weeks	0.00 [0] (17)	0.00 [0] (21)	0.00 [0] (17)	0.00 [0] (21)
	15 weeks	0.00 [0] (16)	0.00 [0] (16)	0.00 [1] (16)	0.00 [0] (17)
	29 weeks	0.00 [1] (16)	0.00 [1] (15)	0.00 [2] (16)	0.00 [1] (15)
	55 weeks	0.00 [1] (11)	0.00 [1] (14)	0.00 [0] (11)	0.00 [0] (14)
Ankle flexion	Baseline	0.00 [0] (22)	0.00 [0] (22)	0.00 [0] (22)	0.00 [0] (23)
	3 weeks	0.00 [0] (17)	0.00 [0] (21)	0.00 [0)] (17)	0.00 [0] (21)
	15 weeks	0.50 [1] (16)	0.00 [2] (16)	1.00 [2] (16)	0.00 [0] (17)
	29 weeks	0.50 [1] (16)	0.00 [0] (15)	0.50 [2] (16)	0.00 [1]) (15)
	55 weeks	0.00 [0] (11)	0.00 [0] (14)	0.00 [2] (11)	0.00 [0] (14)
Ankle extension	Baseline	0.00 [0] (22)	0.00 [0] (22)	0.00 [0] (22)	0.00 [0] (23)
	3 weeks	0.00 [0] (17)	0.00 [0] (21)	0.00 [0] (17)	0.00 [0] (21)
	15 weeks	0.00 [0] (16)	0.00 [0] (16)	0.00 [0] (16)	0.00 [0] (17)
	29 weeks	0.00 [0] (16)	0.00 [0] (15)	0.00 [1] (16)	0.00 [1] (15)
	55 weeks	0.00 [0] (11)	0.00 [0] (14)	0.00 [0] (11)	0.00 [0] (14)

Table 4.17a Proposed Secondary Outcomes

Median knee extensor strength fluctuated in both groups but increased from baseline to 55 weeks. However, the CRF did not distinguish between the paretic and non-paretic leg as shown in Table 4.17a, thus this score includes an average of the paretic and non-paretic legs. Table 4.17b shows that in both groups, participants with left and right hemiparesis increased their strength on both paretic and non-paretic legs from baseline to 55 weeks, with most changes seen in participants with left hemiparesis.

Allocation	Time point	Participants with left hemiparesis median [IQR] (n)		Participants with right hemiparesis median [IQR] (n)	
Intervention group		**LEFT**	**RIGHT**	**LEFT**	**RIGHT**
Knee extensor muscle strength measured in Newtons (maximum score of three trials)	Baseline	44.0 [40] (7)	65 [39] (7)	59 [23] (15)	29 [43] (15)
	3 weeks	77.5 [54] (6)	60.5 [65] (6)	67.0 [33] (11)	51.0 [51] (11)
	15 weeks	96.0 [57] (6)	112.5 [73] (6)	54.0 [30] (9)	27.0 [51] (9)
	29 weeks	90.5 [66] (6)	86.5 [60] (6)	63.5 [30] (10)	49.5 [40] (10)
	55 weeks	113.5 [93] (4)	139.5 [96] (4)	61.0 [28] (7)	39.0 [78] (7)
Control group		**LEFT**	**RIGHT**	**LEFT**	**RIGHT**
Knee extensor muscle strength measured in Newtons (maximum score of three trials)	Baseline	23.0 [52] (11)	71 [35] (11)	67.0 [53] (11)	29.0 [62] (11)
	3 weeks	63.50 [58] (10)	77.0 [39] (10)	69.0 [74] (11)	56.0 [38] (11)
	15 weeks	44.0 [17] (7)	69.0 [20] (7)	73.0 [39] (9)	52.0 [45] (9)
	29 weeks	41.0 [25] (7)	83.0 [31] (7)	77.0 [53] (8)	57.0 [58] (8)
	55 weeks	47.0 [34] (7)	85.0 [39] (7)	81.0 [56] (7)	64.0 [61] (7)

Table 4.17b Knee extensor strength for paretic and non-paretic legs for both groups

The Trunk Control Test scores at baseline were lowest in the intervention group, representing a greater level of impairment. It increased over time and was higher in the intervention group at 55 weeks, compared to the control group (Table 4.17c). However, as with other measures, this may have been influenced by the participant withdrawals.

Some participants were unable to complete the PHQ-9, therefore, a SADQ-10 (observational measure) was completed by a clinician, carer or relative. The number of participants needing a SADQ-10 reduced from baseline to 55 weeks in both groups. PHQ-9 baseline scores were higher in the intervention group suggesting participants in this group had lower mood, and scores reduced at each time point from baseline.

At baseline, more participants were able to complete the multiple-choice questions for EQ-5D-5L than the SAQoL-39. Some participants were unable to complete the health state, which required participants to score their health out of 100.

Outcome variable	**Time point**	**Intervention** median [IQR] (n)	**Control** median [IQR] (n)
Trunk control Test	Baseline	6.0 [15] (22)	12.0 [37] (23)
	3 weeks	25.0 [55] (17)	24.0 [58] (20)
	15 weeks	24.0 [66] (16)	25.0 [61] (17)
	29 weeks	37.0 [37] (16)	18.5 [84] (16)
	55 weeks	25.0 [84] (12)	12.0 [61] (15)
Patient Health Questionnaire 9 (PHQ-9)	Baseline	13.0 [3] (17)	10.0 [10] (19)
	3 weeks	12.0 [10] (16)	8.5 [8] (20)
	15 weeks	13.5 [8] (16)	11.0 [11] (17)
	29 weeks	12.0 [12] (13)	9.0 [6] (16)
	55 weeks	9.0 [9] (11)	8.0 [8] (15)
Stroke Aphasia Depression Questionnaire (SADQ-10)*	Baseline	(5)	(4)
	3 weeks	(1)	(1)
	15 weeks	(0)	(0)
	29 weeks	(3)	(0)

*(n) presented only for 3, 15, 29 and 55 weeks due to insufficient number of participants for mean and IQR	55 weeks	(1)	(0)
Stroke and Aphasia Quality of Life Scale (SAQoL-39)			
Physical	Baseline	1.4 [2.03] (16)	1.8 [1.82] (18)
	3 weeks	3.0 [2.67] (14)	1.8 [1.38] (17)
	15 weeks	1.9 [0.76](15)	2.4 [1.62] (17)
	29 weeks	2.4 [1.96] (14)	2.3 [0.96] (16)
	55 weeks	2.2 [2.00] (11)	2.1 [1.77] (15)
Communication	Baseline	3.0 [3.00] (16)	4.0 [2.07] (18)
	3 weeks	4.0 [2.78] (14)	4.5 [1.36] (17)
	15 weeks	4.3 [2.43] (15)	4.7 [1.00] (17)
	29 weeks	3.8 [2.11] (14)	4.5 [0.68] (16)
	55 weeks	3.9 [2.29] (11)	4.9 [1.43] (15)
Psychosocial	Baseline	3.2 [1.36] (15)	3.3 [1.14] (18)
	3 weeks	3.7 [1.34] (14)	3.6 [0.87] (17)
	15 weeks	3.1 [1.27] (15)	3.9 [0.73] (17)
	29 weeks	3. [1.12] (14)	3.8 [0.80] (16)
	55 weeks	3.3 [1.25] (11)	3.6 [1.27] (15)
Energy	Baseline	3.3 [1.13] (16)	2.9 [1.38] (18)
	3 weeks	3.4 [1.38] (14)	3.3 [1.50] (17)
	15 weeks	3.3 [1.25] (15)	3.5 [1.25] (17)
	29 weeks	3.4 [1.81] (14)	3.3 [1.00] (16)
	55 weeks	3.0 [1.25] (11)	3.3 [1.00] (15)
Total score for all four subgroups	Baseline	2.3 [1.69] (15)	3.1 [1.60] (18)
	3 weeks	3.3 [2.06] (14)	2.7 0.98] (17)
	15 weeks	2.6 [0.46] (15)	3.2 [1.04] (17)
	29 weeks	2.8 1.42] (14)	3.1 [0.60] (16)
	55 weeks	2.8 [0.36] (11)	3.0 [1.08] (15)
European Quality of Life-5 Dimensions (EQ-5D 5L) *Mobility*	Baseline	5.0 [0] (18)	5.0 [0] (21)
	3 weeks	4.5 [3] (14)	5.0 [2] (19)
	15 weeks	5.0 [3] (15)	5.0 [3] (17)
	29 weeks	4.0 [3] (14)	5.0 [2] (16)
	55 weeks	4.0 [3] (11)	3.0 [3] (15)
European Quality of Life-5 Dimensions (EQ-5D 5L) *Self-care*	Baseline	5.0 [2] (18)	4.0 [2] (21)
	3 weeks	3.0 [2] (14)	3.0 [2] (19)
	15 weeks	4.0 [1] (15)	3.0 [3] (17)
	29 weeks	4.0 [2] (14)	4.0 [3] (16)
	55 weeks	4.0 [4] (11)	3.0 [3] (15)
European Quality of Life-5 Dimensions (EQ-5D 5L) *Usual activities*	Baseline	5.0 [3] (18)	5.0 [3] (21)
	3 weeks	3.5 [3] (14)	4.0 [4] (19)
	15 weeks	5.0 [2] (15)	5.0 [2] (17)
	29 weeks	5.0 [3] (14)	5.0 [0] (16)
	55 weeks	5.0 [2] (11)	5.0 [2] (15)

European Quality of Life-5 Dimensions (EQ-5D 5L) *Pain/discomfort*	Baseline 3 weeks 15 weeks 29 weeks 55 weeks	1.0 [2] (18) 1.0 [1] (14) 1.0 [2] (15) 1.0 [2] (14) 2.0 [2] (11)	2.0 [2] (21) 2.0 [2] (19) 3.0 [2] (17) 2.5 [3] (16) 2.0 [4] (15)
European Quality of Life-5 Dimensions (EQ-5D 5L) *Anxiety/depression*	Baseline 3 weeks 15 weeks 29 weeks 55 weeks	2.0 [2] (18) 1.5 [2] (14) 3.0 [1] (15) 2.0 [2] (14) 3.0 [2] (11)	2.0 [3] (21) 1.0 [2] (19) 2.0 [3] (17) 2.0 [2] (15) 2.0 [3] (15)
European Quality of Life-5 Dimensions (EQ-5D 5L) *Health state score Out of 100 where higher score represents improved health*	Baseline 3 weeks 15 weeks 29 weeks 55 weeks	50.0 [50] (17) 50.0 [20] (14) 50.0 [34] (14) 62.5 [39] (10) 54.0 [50] (8)	52.5 [35] (18) 50.0 [43] (17) 50.0 [50] (15) 50.0 [42] (11) 65.0 [38] (14)

Table 4.17c Proposed secondary outcomes

4.11.4 Mean differences between the groups for proposed primary and secondary outcome data

Table 4.18a shows the mean difference between baseline and 3, 15, 29 and 55 weeks for the proposed primary outcome data. For the BI scores, the mean difference between each time point increased in both groups, with the highest scores in the intervention group at 55 weeks. For the Edmans, the mean difference between each time point varied in both groups over all time points. The biggest mean differences were in washing, dressing, meal times and basic mobility from 3 to 55 weeks.

Outcome variable	Treatment Group	Time point			
		3 (+/-1) weeks, mean, SD (n)	15 weeks (+/-1 week), mean, SD (n)	29 weeks (+/-1 week), mean, SD (n)	55 weeks (+/-1 week), mean, SD (n)
Barthel Index	Intervention	5.53, 5.29 (17)	7.0, 6.06 (16)	7.88, 6.88 (16)	8.33, 7.76 (12)
	Control	5.05, 4.67 (22)	6.82, 5.99 (17)	7.69, 6.08 (16)	7.47, 6.44 (15)
	Mean difference (unadjusted analysis)* [95% CI]	0.48 [-2.75, 3.72]	0.17 [-4.10, 4.45]	0.18 [-4.50, 4.88]	0.86 [-4.76, 6.49]
Edmans ADL Index for Stroke	*Intervention*	2.18, 2.53 (17)	2.63, 2.90 (16)	2.63, 3.40 (16)	3.25, 3.77 (12)
	Control	1.77, 2.18 (22)	2.35, 2.26 (17)	2.63, 2.39 (16)	2.33, 2.29 (15)
Washing total	Mean difference (unadjusted analysis)* [95% CI]	0.41 [-1.13, 1.93]	0.27 [-1.57, 2.11]	0.00 [-2.12, 2.12]	0.92 [-1.50, 3.33]
Grooming total	*Intervention*	4.41, 2.81 (17)	5.00, 3.16 (16)	4.50, 3.78 (16)	4.83, 3.81 (12)
	Control	4.23, 3.68 (22)	5.06, 3.78 (17)	5.63, 3.14 (16)	4.93, 3.69 (15)
	Mean difference (unadjusted analysis)* [95% CI]	0.18 [-1.99, 2.36]	-0.59 [-2.54, 2.43]	-1.13 [-3.63, 1.38]	-0.10 [-3.09, 2.89]
Dressing total	*Intervention*	1.82, 2.74 (17)	1.81, 3.02 (16)	2.13, 3.50 (16)	3.08, 4.03 (12)
	Control	1.45, 2.32 (22)	2.00, 2.83 (17)	2.13, 2.96 (16)	2.47, 3.34 (15)
	Mean difference (unadjusted analysis)* [95% CI]	0.37 [-1.28, 2.01]	-0.19 [-2.26, 1.89]	0.00 [-2.34, 2.34]	0.62 [-2.30, 3.53]
Meal times total	*Intervention*	5.06, 3.09 (17)	6.06, 2.91 (16)	6.38, 3.05 (16)	6.83, 2.41 (12)
	Control	5.14, 3.98 (22)	6.94, 2.66 (17)	6.44, 2.99 (16)	6.53, 3.18 (15)

	Mean difference (unadjusted analysis)* [95% CI]	-0.08 [-2.41, 2.26]	-0.88 [-2.86, 1.10]	-0.63 [-2.24, 2.12]	0.30 [-1.99, 2.59]
Basic mobility total	*Intervention*	2.59, 2.76 (17)	3.19, 2.97 (16)	3.94, 3.77 (16)	3.92, 3.82 (12)
	Control	2.05, 2.48 (22)	3.19, 3.59 (17)	3.50, 3.78 (16)	4.13, 4.22 (15)
Advanced mobility total	*Intervention*	1.18, 2.35 (17)	1.56, 3.05 (16)	2.13, 3.34 (16)	2.25, 3.49 (12)
	Control	0.32, 1.09 (22)	1.24, 1.86 (17)	1.69, 2.70 (16)	1.80, 2.43 (15)
	Mean difference (unadjusted analysis)* [95% CI]	0.86 [-0.29, 2.00]	0.33 [-1.45, 2.11]	0.44 [-1.76, 2.63]	0.45 [-1.90, 2.80]
Bed mobility total	*Intervention*	2.06, 2.76 (17)	2.25, 3.32 (16)	3.25, 4.07 (16)	3.50 4.17 (12)
	Control	1.68, 2.46 (22)	2.47, 3.30 (17)	3.00, 3.86 (16)	3.93, 4.37 (15)
	Mean difference (unadjusted analysis)* [95% CI]	0.38 [-1.31, 2.06]	-0.22 [-2.57, 2.13]	0.25 [-2.62, 3.12]	-0.43 [-3.84, 2.98]
Kitchen activities total	*Intervention*	0.65, 1.97 (17)	1.38, 3.07 (16)	1.69, 3.24 (16)	1.17, 2.73 (12)
	Control	0.73, 1.67 (22)	1.59, 2.87 (17)	1.50, 2.53 (16)	1.27, 2.25 (15)
	Mean difference (unadjusted analysis)* [95% CI]	-0.80 [-1.26, 1.10]	-0.21 [-2.33, 1.90]	0.19 [-1.91, 2.29]	-0.10 [-2.07, 1.87]
Housework activities total	*Intervention*	0.41, 1.70 (17)	1.13, 3.07 (16)	1.06, 2.91 (16)	0.92, 2.61 (12)
	Control	0.09, 0.43 (22)	0.18, 0.73 (17)	0.31, 0.87 (16)	0.33, 1.05 (15)
	Mean difference (unadjusted analysis)* [95% CI]	3.21 [-0.44, 1.08]	0.95 [-0.62, 2.51]	0.75 [-0.80, 2.30]	0.58 [-0.93, 2.10]

*calculated using intervention group minus control group. Greater mean differences from baseline = improvement

Table 4.18a Mean difference from baseline (95% Confidence Interval) between both groups at each time point for proposed primary outcome data from baseline

The percentage change from baseline in associated problems for the Edmans (nominal data) is presented in Table 4.18b.

The percentage change fluctuates across all time points for all associated problems.

Outcome variable	Treatment Group	Time point			
		3 weeks (+/-1 week) % (n)	15 weeks (+/-1 week) %(n)	29 weeks (+/-1 week) % (n)	55 weeks (+/-1 week) % (n)
Language problems	*Intervention*	52.9 (9)	62.5 (10)	62.5 (10)	41.7 (5)
	Control	50.0 (11)	35.3 (6)	31.3 (5)	33.3 (5)
	*% difference**	2.9	27.2	31.2	8.4
Perceptual problems	*Intervention*	41.2 (7)	31.3 (5)	37.5 (6)	25.0 (3)
	Control	27.3 (6)	23.5 (4)	25.0 (4)	13.3 (2)
	*% difference**	13.9	7.8	12.5	11.7
Sensory problems	*Intervention*	82.4 (14)	75.0 (12)	87.5 (14)	75.0 (9)
	Control	72.7 (16)	82.4 (14)	68.8 (11)	93.3 (14)
	*% difference**	9.7	-7.4	18.7	-18.3
Dyspraxia problems	*Intervention*	23.5 (4)	6.3 (1)	12.5 (2)	8.3 (1)
	Control	9.1 (2)	0.0 (0)	0.0 (0)	0.0 (0)
	*% difference**	14.4	6.3	12.5	8.3
Reasoning problems	*Intervention*	76.5 (13)	56.3 (9)	75.0 (12)	41.7 (5)
	Control	59.1 (13)	58.8 (10)	50.0 (8)	53.3 (8)
	*% difference**	14.4	6.3	12.5	8.3
Memory problems	*Intervention*	94.1 (16)	81.3 (13)	93.8 (15)	75.0 (9)
	Control	90.9 (20)	94.1 (16)	93.8 (15)	93.3 (14)
	*% difference**	3.2	-12.8	0	-18.3
Depression problems	*Intervention*	35.3 (6)	75.0 (12)	56.3 (9)	66.7 (8)
	Control	18.2 (4)	41.2 (7)	62.5 (10)	46.7 (7)
	*% difference**	17.1	33.8	-6.2	20
Anxiety problems	*Intervention*	23.5 (4)	43.8 (7)	43.8 (7)	25.0 (3)
	Control	45.5 (10)	47.1 (8)	37.5 (6)	33.3 (5)
	*% difference**	-22.0	-3.3	6.3	-8.3

Urinary continence problems	*Intervention*	88.2 (15)	68.8 (11)	62.5 (13)	58.3 (7)
	Control	72.7 (16)	70.6 (12)	81.3(10)	80. (12)
	*% difference**	15.5	-1.8	-18.8	-21.7
Faecal continence problems	*Intervention*	88.2 (15)	56.3 (9)	68.8 (11)	58.3 (7)
	Control	63.6 (14)	76.5 (13)	62.5 (10)	66.7 (10)
	*% difference**	24.6	-20.2	6.3	-8.4

*calculated using intervention group minus control group. Greater mean differences = improvement

Table 4.18b Percentage difference from baseline at each follow up time point for Edmans ADL Index for Stroke Patients Associated Problems

Figure 4.21 suggests greater change in BI score in the intervention group is associated with lower fatigue scores at baseline and higher total standing time, but these relationships are not strong (r = 0.3 total standing time and BI change score; r = -0.2 fatigue score and BI change score).

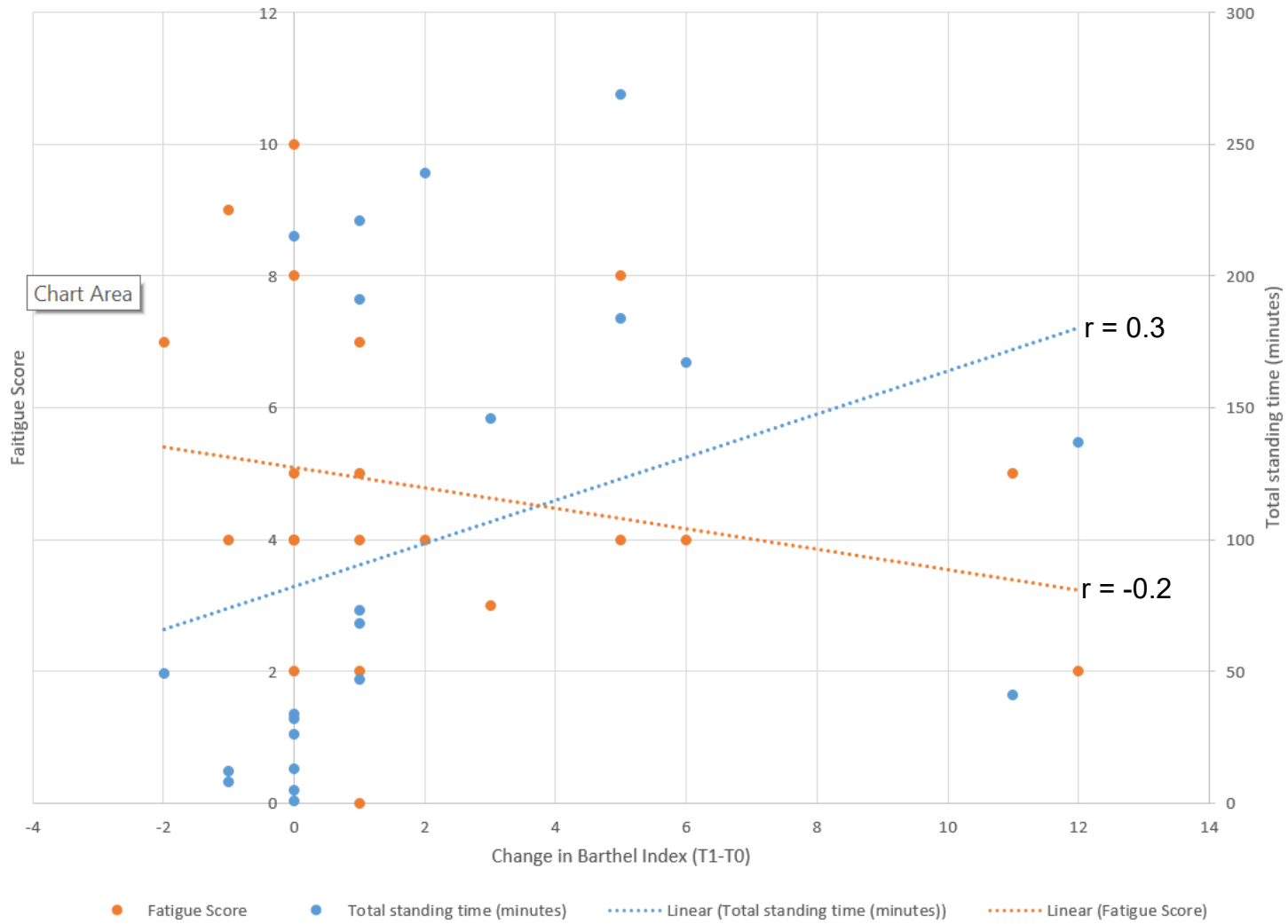


Figure 4.21 Relationship between adherence, fatigue and change in Barthel Index Scores from baseline (T0) to 3 weeks (T1)

The mean change from baseline in the proposed secondary outcome measures at 3, 15, 29 and 55 weeks for muscle length, strength and tone are shown in Tables 4.19a and 4.19b. Both groups vary (mean scores and SD) at all time-points.

		LEFT			RIGHT		
Outcome variable	**Time point** (+/-1 week)	**Intervention** mean, SD (n)	**Control** mean, SD (n)	**Mean Difference (unadjusted analysis)* [95% CI]**	**Intervention** mean, SD (n)	**Control** mean, SD (n)	**Mean Difference (unadjusted analysis)* [95% CI]**
Muscle length using manual goniometry *Hip flexor (Hip angle)*	3 weeks	-0.71, 3.54 (17)	0.5, 3.354 (21)	-0.75 [-3.03 – 1.52]	-1.47, 4.24 (17)	-0,55, 3.649 (20)	-0.92 [-3.55 – 1.71]
	15 weeks	1.20, 9.26 (15)	1.25, 3.69 (16)	-0.05 [-5.15 – 5.07]	0.33, 7.06 (15)	-0.6, 4.93 (16)	0.39 [-4.05 – 4.84]
	29 weeks	2.31, 10.45 (16)	-0.13, 6.20 (15)	2.44 [-3.92 – 8.81]	3.56, 11.94 (16)	-0.40, 5.87 (15)	3.96 [-3.02 – 10.95]
	55 weeks	0.55, 5.68 (11)	2.14, 6.39 (14)	-1.59 [-6.67 – 3.48]	0.91, 8.33 (11)	0.93, 6.01 (14)	-0.19 [-5.95 – 5.91]
Muscle length using manual goniometry *Hamstrings (popliteal angle)*	3 weeks	36.53, 10.93 (17)	36.95, 13.70 (21)	-0.42 [-8.72 – 7.88]	37.06, 10.16 (17)	34.38, 9.29 (21)	2.67 [-3.73 – 9.08]
	15 weeks	40.13, 10.21 (16)	39.56, 5.89 (16)	0.56 [-5.46 – 6.58]	41.5, 10.80 (16)	39.69, 9.98 (16)	1.81 [-5.69 – 9.32]
	29 weeks	40.50, 9.18 (16)	43.13, 9.70 (15)	-2.63 [-9.57 – 4.30]	42.0, 11.55 (16)	42.60, 9.19 (15)	-0.60 [-8.30 – 7.10]
	55 weeks	42.55, 8.99 (11)	42.7, 8.34 (14)	-0.16 [-7.36 – 7.02]	44.73, 7.57 (11)	43.36, 8.41 14	1.37 [-5.35 – 8.09]
Muscle length using manual goniometry	3 weeks	-4.1, 3.80 (17)	-2.10, 4.56 (21)	1.68 [-1.12 – 4.49]	-0.71, 10.92 17	-1.95, 6.087 (21)	1.24 [-4.31 – 6.92]

Ankle dorsi flexion (ankle dorsi flexion angle)	15 weeks	-0.56, 6.76 (16)	0.00, 5.91 (17)	-0.56 [-5.06 – 3.94]	0.50, 8.92 (16)	-2.71, 4.51 (17)	3.20 [-1.77 – 8.18]
	29 weeks	-2.31, 7.65 (16)	-2.20, 8.18 (15)	-.0.11 [-5.93 – 5.70]	1.00, 11.14 (16)	-1.80, 6.88 (15)	2.80 [-4.06 – 9.66]
	55 weeks	-1.55, 7.27 (11)	6.93, 20.53 (14)	-8.47 [-21.94 – 5.00]	0.09, 11.60 (11)	3.14, 15.86 (15)	-3.05 [-14.86 – 8.76]
Muscle length using manual goniometry	3 weeks	42.84, 6.95 (17)	40.33, 7.80 (21)	2.49 [-2.42 – 7.41]	37.59, 12.95 (17)	41.33, 8.02 (21)	-3.74 [-10.69 – 3.20]
Ankle plantar flexion (ankle plantar flexion angle)	15 weeks	40.44, 6.64 (16)	33.53, 9.24 (17)	6.90 [1.15 – 12.65]	39.33, 8.46 (15)	33.24, 9.07 (17)	6.09 [-0.23 – 12.46]
	29 weeks	41.25, 7.93 (16)	37.07, 8.47 (15)	4.18 [-1.84 – 10.21]	41.63, 6.27 (16)	37.67, 8.26 (15)	3.95 [-1.40 – 9.32]
	55 weeks	39.91, 10.38 (11)	35.57, 15.05 (14)	4.33 [-6.93 – 15.60]	36.36, 8.62 (11)	34.50, 15.07 (14)	1.86 [-8.70 – 12.43]
Knee muscle strength measured in Newtons (Maximum score of three trials)	3 weeks	17, 68.59 (27.38)	21, 59.71 (34.15)	8.87 [-11.85 – 29.60]	17, 59.82 (32.95)	21, 60.19 (24.67)	-0.36 (-19.32 – 18.59)
	15 weeks	15, 70.33 (25.43)	16, 59.19 (25.89)	11.14 [-7.69 – 29.98]	15, 67.00 (42.07)	16, 60.06 (24.88)	6.93 (-18.25 – 32.13)
	29 weeks	16, 71.69 (28.25)	15, 60.20 (35.21)	11.48 [-11.89 – 34.86]	16, 59.81 (34.77)	15, 69.73 (35.39)	-9.92 (-35.70 – 15.86)
	55 weeks	11, 79.00 (38.10)	14, 67.07 (43.86)	11.92 [-22.62 – 46.48]	11, 80.27 (55.20)	14, 69.36 (32.27)	10.91 (-25.54 – 47.37)
Modified Ashworth Scale Score	3 weeks	17, 0.06 (0.24)	21, 0.24 (0.54)	-0.18 [-0.47 – 0.11]	17, 0.12 (0.33)	21, 0.19 (0.51)	-0.73 [-0.37 – 0.22]
Hip adductors	15 weeks	16, 0.19 (0.54)	16, 0.31 (0.60)	-0.13 [-0.54 – 0.29]	16, 0.25 (0.57)	17, 0.12 (0.33)	0.13 [-0.20 – 0.46]
	29 weeks	16, 0.50 (1.10)	15, 0.40 (0.74)	0.10 [-0.59 – 0.79]	16, 0.75 (1.24)	15, 0.406 (0.74)	0.35 [-0.40 – 0.79]
	55 weeks	11, 0.36 (0.51)	14, 0.50 (0.86)	0.14 [-0.74 – 0.47]	11, 0.27 (0.65)	14, 0.50 (1.02)	-0.23 [-0.96 – 0.50]

Hamstrings	3 weeks	17, 0.12 (0.49)	21, 0.19 (0.68)	-0.73 [0.47 0 – 0.33]	17, 0.06 (2.43)	21, 0.19 (0.51)	-0.13 [-0.41 – 0.14]
	15 weeks	16, 0.31 (0.87)	16, 0.25 (0.58)	0.06 [-0.47 – 0.60]	16, 0.50 (0.96)	17, 0.12 (0.33)	0.38 [-0.12 – 0.89]
	29 weeks	16, 0.50 (0.89)	15, 0.47 (0.74)	0.33 [-0.57 – 0.64]	16, 0.75 (1.00)	15, 0.60 (0.74)	0.15 [-0.50 – 0.80]
	55 weeks	11, 0.36 (0.67)	14, 0.50 (0.94)	0.14 [-0.83 – 0.56]	11, 0.36 (0.92)	14, 0.43 (0.94)	-0.07 [-0.84 – 0.71]
Ankle flexion	3 weeks	17, 0.18 (0.73)	21, 0.29 (0.64)	-0.11 [-0.56 – 0.34]	17, 0.24 (0.97)	21, 0.14 (0.48)	0.92 [-0.39 – 0.58]
	15 weeks	16, 0.69 (0.87)	16, 0.69 (1.01)	0.00 [-0.68 – 0.68]	16, 1.13 (1.30)	17, 0.59 (1.32)	0.54 [-0.38 – 1.46]
	29 weeks	16, 0.63 (0.72)	15, 0.40 (0.91)	0.23 [-0.88 – 0.83]	16, 1.06 (1.34)	15, 0.53 (0.99)	0.53 [-0.34 – 1.40]
	55 weeks	11, 0.82 (1.25)	14, 0.50 (1.09)	0.45 [(-0.91 – 1.00]	11, 0.82 (1.25)	14, 0.50 (1.09)	0.32 [-0.65 – 1.29]
Ankle extension	3 weeks	17, 0.12 (0.49)	21, 0.14 (0.48)	-0.02 [-0.34 – 0.29]	17, 0.24 (0.97)	21, 0.14 (0.48)	0.92 [-0.40 – 0.58]
	15 weeks	16, 0.25 (0.78)	16, 0.25 (0.57)	0.00 [-0.49 – 0.49]	16, 0.38 (1.03)	17, 0.29 (0.70)	0.08 [-0.54 – 0.70]
	29 weeks	16, 0.38 (0.89)	15, 0.13 (0.35)	0.24 [-0.26 – 0.74]	16, 0.50 (1.03)	15, 0.00 (0.00)	0.50 [-0.05 – 1.05]
	55 weeks	11, 0.00 (0.00)	14, 0.43 (1.09)	-0.43 [-1.11 – 0.25]	11, 0.36 (0.92)	14, 0.29 (0.72)	0.78 [-0.60 – 0.76]

* calculated using intervention group minus control group CI = confidence interval

Table 4.19a Mean difference (95% Confidence Interval) between the groups at each time point for proposed secondary outcome data from baseline

Table 4.19b shows the change from baseline in proposed secondary outcome data for the Trunk Control Test and patient-report outcome measures from baseline for both groups. Trunk Control Test scores had wide 95% confidence intervals and scores were similar for both groups. Scores were also similar in both groups for PHQ-9, SAQoL-39, EQ-5D-5L. For the SAD-Q10, there was only one participant for all time points except 29 weeks, therefore, there is no indication of variance (SD) provided.

Outcome variable	**Time point** (+/-1 week)	**Intervention group** Mean, SD (n)	**Control group** Mean, SD (n)	**Mean Difference (unadjusted analysis)* [95% CI]**
Trunk Control Test	3 weeks	33.24, 33.40 (17)	31.85, 30.96 (20)	1.38 (-20.11 – 22.88)
	15 weeks	35.50, 37.67 (16)	33.35, 34.80 (17)	2.14 (-23.58 – 27.88)
	29 weeks	37.88, 33.94 (16)	37.06, 38.53 (16)	0.81 (-25.10 – 26.73)
	55 weeks	36.25, 40.77 (12)	32, 37.77 (15)	4.25 (-26.96 – 35.46)
Patient Health Questionnaire 9 (PHQ-9)	3 weeks	11.69, 5.52 (16)	10.55, 4.77 (20)	1.13 (-2.35 – 4.62)
	15 weeks	13.69, 4.75 (16)	10.82, 6.44 (17)	2.86 (-1.17 – 6.90)
	29 weeks	9.85, 6.84 (13)	8.69, 4.19 (16)	1.15 (-3.07 – 5.39)
	55 weeks	8.82, 5.17 (11)	9.07, 6.13 (15)	-2.48 (-4.84 – 4.46)
Stroke Aphasia Depression Questionnaire (SAD-Q10)	3 weeks	14.00, 0.00 (1)	12, 0.00 (1)	2.00, 0.00 (1)
	15 weeks	14.00, 0.00 (1)	12, 0.00 (1)	2.00, 0.00 (1)
	29 weeks	12.00, 8.66 (3)	(0)	-
	55 weeks	17.00, 0.00 (1)	(0)	-
Stroke and Aphasia Quality of Life Scale (SAQOL39) Subgroup: Physical	3 weeks	2.92, 1.27 (14)	2.23, 1.12 (17)	0.68 (-0.20 – 1.56)
	15 weeks	2.19, 0.96 (15)	2.47, 0.99 (17)	-0.27 (-0.98 – 0.43)
	29 weeks	2.53, 1.28 (14)	2.32, 0.74 (16)	0.27 (-0.56 – 0.97)
	55 weeks	2.33, 1.16 (11)	2.31, 1.03,) (15)	0.15 (-0.88 – 0.91)
	3 weeks	3.66, 1.35 (14)	4.22, 0.93 (17)	-0.56 (-1.4 – 0.28)

Stroke and Aphasia Quality of Life Scale (SAQOL39) Subgroup: Communication	15 weeks	3.64, 1.27 (15)	4.3, 0.78 (17)	-0.71 (-1.46 – 0.41)
	29 weeks	3.68, 1.10 (14)	4,57, 0.39 (16)	-0.88 (-1.49 – 0.28)
	55 weeks	3.84, 1.21 (11)	4.29, 0.79 (15)	0.26 (-1.26 – 0.36)
Stroke and Aphasia Quality of Life Scale (SAQOL39) Subgroup: Psychosocial	3 weeks	3.55, 0.83 (14)	3.54, 0.74 (17)	0.01 (-0.56 – 0.59)
	15 weeks	3.22, 0.71 (15)	3.75, 0.65 (17)	-0.52 (-1.02 – -0.02)
	29 weeks	3.46, 0.80 (14)	3.53, 0.64 (15)	-0.17 (-0.71 – 0.36)
	55 weeks	3.31, 0.79 (11)	3.47, 0.76 (15)	-0.16 (-0.80 – 0.47)
Stroke and Aphasia Quality of Life Scale (SAQOL39) Subgroup: Energy	3 weeks	3.21, 0.89 (14)	3.30, 0.95 (17)	-0.94 (-0.78 – 0.59)
	15 weeks	3.46, 0.66 (15)	3.44, 0.84 (17)	0.02 (-0.52 – 0.57)
	29 weeks	3.39, 1.05 (14)	3.37, 0.81 (16)	0.01 (-0.68 – 0.72)
	55 weeks	3.11, 0.82 (11)	3.30, 0.66 (15)	-0.18 (-0.78 – 0.41)
Stroke and Aphasia Quality of Life Scale (SAQOL39)	3 weeks	3.26, 1.00 (14)	3.07, 0.77 (17)	0.19 (-0.45 – 0.84)
	15 weeks	2.87, 0.60 (15)	3.27, 0.60 (17)	-0.39 (-0.86 – 0.78)
	29 weeks	3.09, 0.94 (14)	3.20, 0.43 (16)	-0.11 (-0.64 – 0.42)
	55 weeks	2.95, 0.76 (11)	3.10, 0.64 (15)	-0.14 (-0.71 – 0.42)
European Quality of Life-5 Dimensions (EQ-5D 5L) Mobility	3 weeks	3.79, 1.47 (14)	3.79, 1.61 (19)	-0.04 (-1.12 – 1.11)
	15 weeks	3.67, 1.65 (15)	3.71, 1.72 (17)	-0.03 (-1.25 – 1.17)
	29 weeks	3.43, 1.45 (14)	4.00, 1.26 (16)	-0.57 (-1.58 – 0.44)
	55 weeks	3.82, 1.32 (11)	3.33, 1.63 (15)	0.48 (-0.75 – 1.72)
European Quality of Life-5 Dimensions (EQ-5D 5L) Self-care	3 weeks	3.21, 1.36 (14)	2.95, 1.39 (19)	0.26 (-0.72 – 1.26)
	15 weeks	3.40, 1.29 (15)	3.00, 1.50 (17)	0.40 (-0.62 – 1.42)
	29 weeks	3.43, 1.32 (14)	3.56, 1.59 (16)	-0.13 (-1.24 – 0.97)
	55 weeks	3.36, 1.80 (11)	3.47, 1.40) (15)	-0.10 (-1.40 – 1.19)
European Quality of Life-5 Dimensions (EQ-5D 5L) Usual activities	3 weeks	3.36, 1.59 (14)	3.32, 1.79 (19)	0.41 (-1.19 – 1.27)
	15 weeks	4.07, 1.43 (15)	4.18, 1.28 (17)	-0.10 (-.09 – 0.87)
	29 weeks	3.86, 1.70 (14)	4.44, 1.26 (16)	-0.58 (-1.69 – 0.53)
	55 weeks	4.09, 1.38 (11)	4.07, 1.38 (15)	0.24 (-1.13 – 1.18)

European Quality of Life-5 Dimensions (EQ-5D 5L) Pain/discomfort	3 weeks	1.64, 1.27 (14)	1.89, 0.99 (19)	-0.25 (-1.05 – 0.55)
	15 weeks	1.87, 1.12 (15)	2.35, 1.11 (17)	-0.486 (-1.29 – 0.32)
	29 weeks	19.3, 1.32 (14)	2.44, 1.45 (16)	-0.50 (-1.55 – 0.54)
	55 weeks	2.09, 1.30 (11)	2.60, 1.72 (15)	-0.50 (-1.78 – 0.77)
European Quality of Life-5 Dimensions (EQ-5D 5L) Anxiety/depression	3 weeks	2.07, 1.26 (14)	1.74, 1.24 (19)	0.22 (-0.56 – 1.23)
	15 weeks	2.47, 0.99 (15)	2.47, 1.50 (17)	-0.004 (-0.93 – 0.93)
	29 weeks	2.29, 1.38 (14)	2.33, 1.29 (15)	-0.48 (-1.07 – 0.97)
	55 weeks	2.27, 0.90 (11)	2.40, 1.50 (15)	-0.12 (-1.18 – 0.92)
European Quality of Life-5 Dimensions (EQ-5D 5L)	3 weeks	50.71, 20.17 (14)	55.59, 23.97 (17)	-4.87 (-21.37 – 11.62)
	15 weeks	50.14, 24.35 (14)	48.00, 26.78,) (15)	2.14 (-17.40 – 21.69)
	29 weeks	60.00, 31.35 (10)	53.45, 27.22 (11)	7.54 (-19.21 – 34.30)
	55 weeks	52.25, 25.16 (8)	57.50, 27.99 (14)	-5.25 (-30.24 – 19.74)

* calculated by intervention group minus control group

Table 4.19b Mean difference (95% Confidence Interval) between the groups at each time point for proposed secondary outcome data from baseline

4.11.5 Timing of assessments

The target was to complete the baseline assessments within ± seven days of consent and all other visits within ± seven days of the dates stipulated on the trial website (calculated from date of randomisation). Table 4.20 shows the timing of assessments throughout the trial. One participant was unwell for their baseline assessment, which was completed within 14 days, resulting in 97.8% (n=44) baseline assessments completed within target. In all cases and at all time-points, the assessments were not completed within this protocolised time frame because the participants had withdrawn from the trial.

However, when removing participants who withdrew, the completion rates are much higher for 15, 29 and 55 weeks, as shown at the bottom of Table 4.20.

	Baseline (n=45*) (T1) % (n)	3 weeks (T2) (n=39*) % (n)	15 weeks (T3) (n=33*) % (n)	29 weeks (T4) (n=32*) % (n)	55 weeks T5) (n=27*) % (n)
Completion status including withdrawals					
Completed within 7 days of consent or ± 7 days from the follow-up visit date as per protocol[351]	97.8 (44)	82.2 (37)	73.3 (33)	71.1 (32)	55.6 (25)
Completed within +/- 8-14 days of consent or ± 7 days from the follow-up visit date as per protocol[351]	2.2 (1)	4.4 (2)	0.00 (0)	0.00 (0)	4.4 (2)
Not completed	0.00 (0)	13.3 (6) [n=6 withdrawn]	26.6 (12) [n=11 withdrawn, n=1 unavailable]	13.3 (13) [n=13 withdrawn]	40.0 (18) [n=18 withdrawn]
Completion status excluding withdrawals					
Completed within 7 days of consent or ± 7 days from the follow-up visit date as per protocol[351]	97.8 (44)	94.9 (37)	100.0 (33)	100.0 (32)	92.6 (25)
Completed within +/- 8-14 days of consent or ± 7 days from the follow-up visit date as per protocol[351]	2.2 (1)	5.1 (2)	0.00 (0)	0.00 (0)	7.4 (2)

*number participants in the trial at each time-point

Table 4.20 Timing of assessments

4.12 Missing data

Missing data for the proposed primary outcome measures is shown in Tables 4.21.. There are more missing data in the intervention group, which increased at week 3, 15 and 55. Both proposed primary outcome measures have the same

percentage of completeness. With exception of the participants who withdrew, all but one participant completed their primary outcome measures (one participant in the intervention group was unwell and missed their 3-week visit).

Outcome Variable	Time point	Completeness of Outcome Measure out of 45 participants % (n)	% (n) missing	
			Intervention	Control
Barthel Index	Baseline	100.0 (45)	0 (0)	0 (0)
	Week 3	87.0 (39)	22.7 (5)	4.3 (1)
	Week 15	73.3 (33)	27.3 (6)	26.1 (6)
	Week 29	71.1 (32)	27.3 (6)	30.4 (7)
	Week 55	60.0 (27)	45.5 (10)	34.8 (8)
Edmans Activities of Daily Living Index for Stroke Patients	Baseline	100.0 (45)	0 (0)	0 (0)
	Week 3	87.0 (39)	22.7 (5)	4.3 (1)
	Week 15	73.3 (33)	27.3 (6)	26.1 (6)
	Week 29	71.1 (32)	27.3 (6)	30.4 (7)
	Week 55	60.0 (27)	45.5 (10)	34.8 (8)

Table 4.21a Summary of missing data for proposed primary outcome measures

Due to participant withdrawals and deaths, the number of physical secondary outcomes measures completed dropped at each timepoint from baseline in both groups (intervention group: 100% at baseline to 50% at week-55; control group: 95.7% at baseline to 60.90% at week-55). The number of participants able to complete the PHQ-9 increased over time, thus the number of SADQ-10 reduced over time. However, comparing participants' responses over time was affected by switching from one measure to another during follow-up periods. At baseline, more participants were able to complete the EQ-5D-5L than the

SAQoL-39. However, completeness of the EQ-5D-5L got worse over time for the health state. Blinded assessor 1 (CI) captured reasons why outcome assessments were not undertaken or completed, but this was not formally requested therefore was not captured for Blinded Assessor 2. Reasons for non-completion for all or component parts of physical outcome measures were pain, ankle fracture, fatigue, did not want to lay flat, did not want to be moved, and cognitive and/or communication impairment, not wanting to answer a specific question (n=1 participant, one question in EQ-5D-5L about depression) for self-report outcome measures.

Outcome Variable	**Time point**	**Completeness of Outcome Measure out of 45 participants % (n)**		**% (n) missing**	
		Intervention	Control	Intervention	Control
PHQ-9	Baseline	77.3 (17)	82.6 (19)	22.7 (5) [completed SADQ10]	17.4 (4) [completed SADQ10]
	Week 3	72.7 (16)	87.0 (20)	27.3 (6) [n=1 completed SAD10, n=1 unwell, n=4 withdrawn]	13.0 (3) [n=1 completed SADQ10 [n=2 withdrawn]
	Week 15	72.7 (16)	73.9 (17)	27.3 (6) [all withdrawn]	26.1 (6) [n=1 unavailable, n=5 withdrawn]
	Week 29	59.1 (13)	69.6 (16)	40.9 (9) [n=3 completed SADQ10, n=6 withdrawn]	30.4 (7) [all withdrawn]
	Week 55	50.0 (11)	65.2 (15)	50.0 (11) [n=1 completed SADQ10, [n=10 withdrawn]	34.8 (8) [all withdrawn]
SAD-Q10	Baseline	22.7 (5)	17.4 (4)	72.3 (17)	82.6 (19)
	Week 3	4.5 (1)	4.3 (1)	72.7 (16)	86.9 (20)

This measure was only completed if participants were unable to complete the PHQ-9 due to aphasia	Week 15 Week 29 Week 55	0.0 (0) 13.6 (3) 4.5 (1)	0.0 (0) 0.0 (0) 0.0 (0)	100.0 (22) 86.4 (19) 95.5 (21)	100.0 (23) 100.0 (23) 100.0 (23)
SAQoL-39 Physical score	Baseline Week 3 Week 15 Week 29 Week 55	72.7 (16) 63.6 (14) 68.2 (15) 63.6 (14) 50.0 (11)	78.3 (18) 73.9 (17) 73.9 (17) 69.6 (16) 65.2 (15)	27.3 (6) 36.4 (8) 31.8 (7) 36.4 (8) 50.0 (11)	21.7 (5) 26.1 (6) 26.1 (6) 30.4 (7) 34.8 (8)
SAQoL-39 Communication score	Baseline Week 3 Week 15 Week 29 Week 55	72.7 (16) 63.6 (14) 68.2 (15) 63.6 (14) 50.0 (11)	78.3 (18) 73.9 (17) 73.9 (17) 69.6 (16) 65.2 (15)	27.3 (6) 36.4 (8) 31.8 (7) 36.4 (8) 50.0 (11)	21.7 (5) 26.1 (6) 26.1 (6) 30.4 (7) 34.8 (8)
SAQoL-39 Psychosocial score	Baseline Week 3 Week 15 Week 29 Week 55	72.7 (16) 63.6 (14) 68.2 (15) 63.6 (14) 50.0 (11)	78.3 (18) 73.9 (17) 73.9 (17) 69.6 (16) 65.2 (15)	27.3 (6) 36.4 (8) 31.8 (7) 36.4 (8) 50.0 (11)	21.7 (5) 26.1 (6) 26.1 (6) 30.4 (7) 34.8 (8)
SAQoL-39 Energy score	Baseline Week 3 Week 15 Week 29 Week 55	72.7 (16) 63.6 (14) 68.2 (15) 63.6 (14) 50.0 (11)	78.3 (18) 73.9 (17) 73.9 (17) 69.6 (16) 65.2 (15)	27.3 (6) 36.4 (8) 31.8 (7) 36.4 (8) 50.0 (11)	21.7 (5) 26.1 (6) 26.1 (6) 30.4 (7) 34.8 (8)
EQ-5D-5L Mobility	Baseline Week 3 Week 15 Week 29	81.8 (18) 63.6 (14) 68.2 (15) 63.6 (14)	91.3 (21) 82.6 (19) 73.9 (17) 69.6 (16)	18.2 (4) 36.4 (8) 31.8 (7) 36.4 (8)	8.7 (2) 17.4 (4) 26.1 (6) 30.4 (7)

	Week 55	50.0 (11)	65.2 (15)	50.0 (11)	34.8 (8)
EQ-5D-5L	Baseline	81.8 (18)	91.3 (21)	18.2 (4)	8.7 (2)
Self-care	Week 3	63.6 (14)	82.6 (19)	36.4 (8)	17.4 (4)
	Week 15	68.2 (15)	73.9 (17)	31.8 (7)	26.1 (6)
	Week 29	63.6 (14)	69.6 (16)	36.4 (8)	30.4 (7)
	Week 55	50.0 (11)	65.2 (15)	50.0 (11)	34.8 (8)
EQ-5D-5L	Baseline	81.8 (18)	91.3 (21)	18.2 (4)	8.7 (2)
Usual activities	Week 3	63.6 (14)	82.6 (19)	36.4 (8)	17.4 (4)
	Week 15	68.2 (15)	73.9 (17)	31.8 (7)	26.1 (6)
	Week 29	63.6 (14)	69.6 (16)	36.4 (8)	30.4 (7)
	Week 55	50.0 (11)	65.2 (15)	50.0 (11)	34.8 (8)
EQ-5D-5L	Baseline	81.8 (18)	91.3 (21)	18.2 (4)	8.7 (2)
Pain/Discomfort	Week 3	63.6 (14)	82.6 (19)	36.4 (8)	17.4 (4)
	Week 15	68.2 (15)	73.9 (17)	31.8 (7)	26.1 (6)
	Week 29	63.6 (14)	69.6 (16)	36.4 (8)	30.4 (7)
	Week 55	50.0 (11)	65.2 (15)	50.0 (11)	34.8 (8)
EQ-5D-5L	Baseline	81.8 (18)	91.3 (21)	18.2 (4)	8.7 (2)
Anxiety/Depression	Week 3	63.6 (14)	82.6 (19)	36.4 (8)	17.4 (4)
	Week 15	68.2 (15)	73.9 (17)	31.8 (7)	26.1 (6)
	Week 29	63.6 (14)	69.6 (16)	36.4 (8)	34.8 (8)
	Week 55	50.0 (11)	65.2 (15)	50.0 (11)	34.8 (8)
EQ-5D-5L	Baseline	77.3 (17)	78.3 (18)	22.7 (5)	21.7 (5)
Health State	Week 3	63.6 (14)	65.2 (15)	36.4 (8)	26.1 (6)
	Week 15	63.6 (14)	65.2 (15)	36.4 (8)	34.8 (8)
	Week 29	45.5 (10)	47.8 (11)	54.5 (12)	52.2 (12)
	Week 55	36.4 (8)	60.9 (14)	63.6 (14)	39.1 (9)

Table 4.21b Summary of missing data for proposed secondary patient report outcome measures

4.13 Blinding

The CI was unblinded to 10 participants after the 3-week assessment for the purpose of interview. The CRF asked whether the assessor was unblinded during the visit, instead of prior to or during the visit for the 15-, 29- and 55-week assessments, therefore, this was frequently answered as not unblinded during the visit. There were no other instances of unblinding during or between visits other than the 10 participants who were interviewed, and Blinded Assessor 2 was not unblinded. Table 4.22 shows the extent to which the assessors remained blinded. The number of instances the blinded assessors guessed group allocation correctly was higher than chance.

Follow-up time point post-randomisation	Number of assessments completed (n)	Number of instances the blinded assessor believed they had been unblinded % (n)	Number of instances the blinded assessor correctly guessed group allocation % (n)
3 weeks	38	0.00 (0)	65.8 (25)
15 weeks	33	5.98 (3)	75.6 (25)
29 weeks	32	3.12 (1)	68.8 (22)
55 weeks	27	0.00 (0)	74.1 (20)

Table 4. 22 The extent to which the assessors remained blinded

4.14 Responsiveness of proposed outcome measures

Responsiveness, or sensitivity to change, of the proposed outcome measures will be addressed in the discussion chapter (Chapter 5). Caution needs to be applied when looking at responsiveness over time because this feasibility trial is not powered for this purpose. Looking at the primary outcome measures in Table 4.16a (Section 4.12), BI scores initially increase, followed by a slow steady increase which then plateaus. Table 4.16a included the whole dataset, i.e. participants who did not complete all follow-up assessments that may skew

the results. Figure 4.22 below shows the change scores for the 27 participants who completed assessments at all time points to show responsiveness.

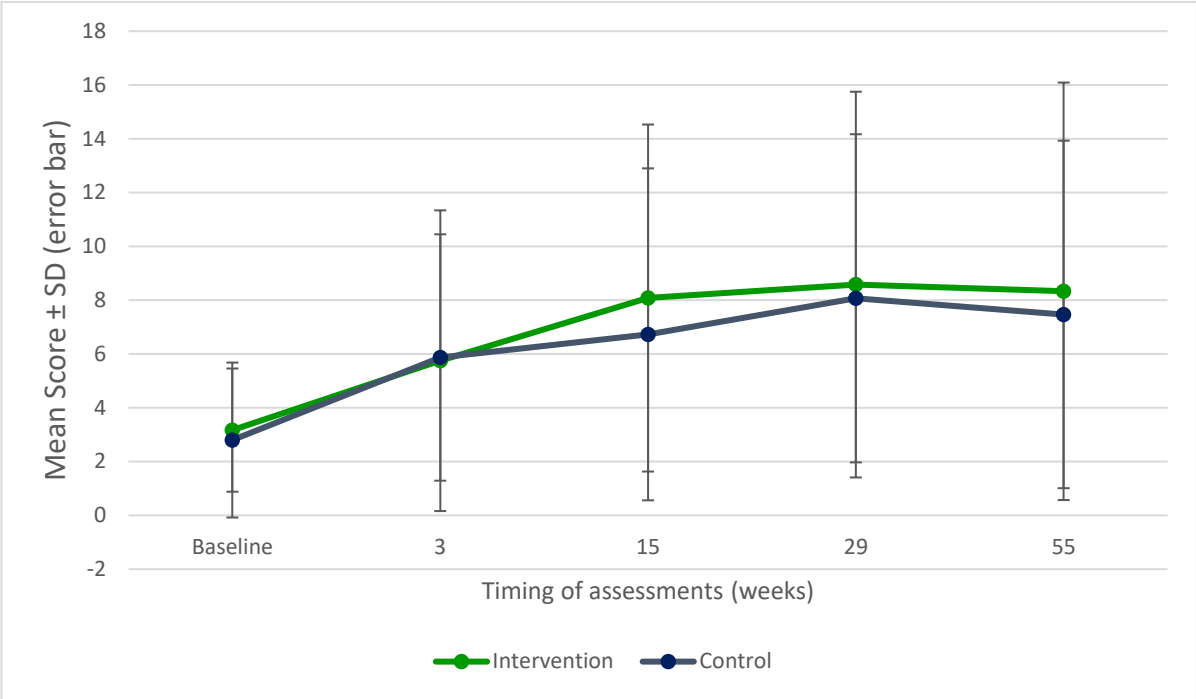


Figure 4.22 Change scores for the Barthel Index for the 27 participants who completed assessments at all time-points for both groups

The Edmans showed a similar pattern of changes to the BI, with the largest increase in scores from baseline to 3-weeks, and a smaller change between 15 and 29 weeks. There is no overall score for the Edmans, each domain is scored separately. Scores increased (indicating improvement) at each of the five time points for washing (0.73 to 3.25), dressing (0.42 to 4.83) and kitchen activities (0 to 3.93) . Subgroups with the greatest difference between groups were advanced mobility 0 to 2.25) (difference seen as early as three weeks 0 at baseline 1.5 week-3) and housework activities (0 to 1.5). There was no difference in grooming (combing hair, cleaning teeth and shaving) which was not expected.

Except for basic mobility, advanced mobility and bed mobility, the activities in other subgroups can be carried out in either sitting or standing, thus, an outcome measure of mobility for a subsequent trial may preferable.

Secondary outcome measures, such as muscle length did not show any marked changes over the period and all changes were less than 3 degrees. However, it is unclear whether this reflects a lack of responsiveness of the outcome measures or a lack of clinical improvement in this feasibility trial. The Trunk Control Test showed the potential to detect change (Figure 4.23) which would justify its use in a subsequent main trial, however, this measures trunk control in lying and sitting, standing is not included. Caution needs to be applied because the sample size is not powered for the purpose of determining a change between the two groups. Figure 4.23 includes assessment data for the 27 participants who completed the trial.

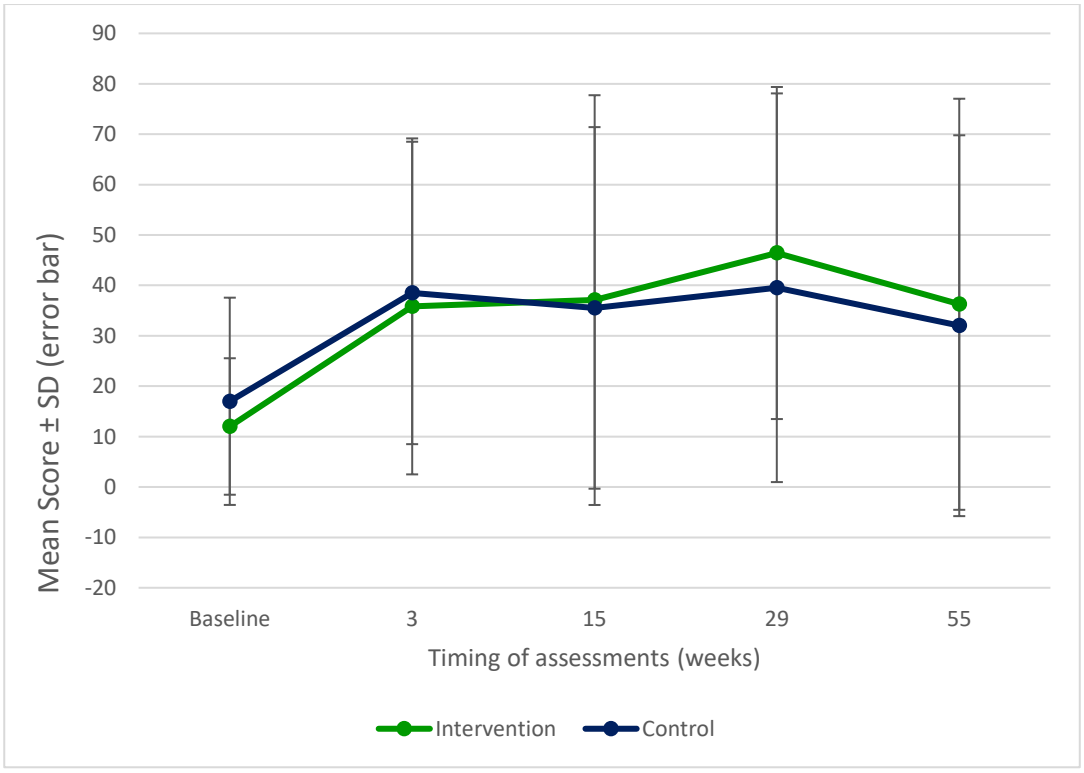


Figure 4.23 Change scores for the Trunk Control Test change for the 27 participants who completed assessments at all time-points for both groups

4.15 Endpoint

Assessment of the change in outcome measures over time highlights that any change between groups is evident by 29 weeks and does not tend to increase thereafter. The plateau in outcome measures from 29-55 weeks suggests that a follow-up at 29 weeks for a subsequent trial will suffice. The discussion (Chapter 5) will explore which outcome measure may be suitable.

4.16 Sample size

This feasibility trial has produced the necessary parameter estimates (e.g. standard deviations of a chosen [continuous] primary outcome) which can be used to calculate effect sizes and produce a sample size for a future main trial. However, the feasibility objectives (Tables 4.23 and 4.24) suggest that the trial will not progress in its current design, therefore, sample size calculations have not been undertaken.

4.17 Feasibility objectives

The feasibility objectives have been addressed and are shown in Table 4.23. Many of the objectives were demonstrated to be feasible: recruitment, retention and consent rate, eligibility criteria, burden, fidelity, orthostatic hypotension protocol and safety. Willingness of physiotherapists to recruit, willingness of patients to be randomised and acceptability of the intervention are described in more detail in the qualitative data (Section 4.24) and discussed in Chapter 5. Participant adherence to the intervention group was not achieved by any participant. This is described in more detail in the qualitative data (Section 4.24) and discussed in Chapter 5.

Feasibility Indicator	Outcome Measures and Results	Parameter for Success	Feasible (Y/N)	Suggested Modification
Process				
Recruitment rate	7.6% of participants admitted across all four SRUs were recruited 90% of the target 50 participants were recruited	≥70% of 50 participants over 13 months (Scenario 1 from the Statistical Analysis Plan)	Y	
Retention rate	***Allocated groups*** T1 100% intervention, 100% control T2 77.2% intervention, 91.3% control T3 72.7% intervention, 91.3% control T4 72.7% intervention, 69.6% control T5 54.5% intervention, 65.2% control ***Groups combined*** T1 100.0% (n=45)	60% of participants completed T1, T2, T3, T4, T5 (this includes an estimated 40% drop out rate due to mortality). (Scenario 1 from the Statistical Analysis Plan)	Y	Need to account for higher mortality rate and reduce follow-up period to 6 months

	T2 77.8% (n=38) T3 73.3% (n=33 T4 71.1% (n=32 T5 60.0% (n=27)			
Ability to consent	63.0% (n=29) participants provided informed consent		Y	
Consent rate	78.0% (n=46 consented divided by n=59 eligible)		Y	
Eligibility criteria	Scenario 1 (initial screen on admission to SRU): 79.0% of admissions screened (462/586) 91.8% eligible participants approached (73 screened minus n=2 died and n=4 staff shortage; 67 divided by 73 multiplied by 100) Scenario 2: (formal screening by completing a Screening CRF once stroke severity confirmed eligible) 59.3% screened (n=73 divided by 123: 586 admitted minus 462 not eligible = 124 minus 1 died = 123) 63.0 % eligible (46 divided by 73 multiplied by 100)	≥50% of admissions screened and ≥75% of eligible participants approached ≥50% of admissions screened and ≥75% of eligible participants approached	Y Y	Need to take into account reasons not enrolled (staff shortages, missed not screened, site not actively recruiting) and implement trial processes to address these issues, e.g. network or R&D clinicians identifying and consenting participants.
Willingness of physiotherapists to recruit	92% of admissions pre-screened for stroke severity (n=586 admitted: n=13 missed, n=5 staff shortage, n=2 no reasons given, n=27 site not actively recruiting equals n=539 screened)	≤10% of participants not approached	Y	

	81% eligible participants approached			
Willingness of patients to be randomised	11.9% of eligible participants declined to enrol in the trial (n=73 screened, n=59 eligible, n=7 declined to enrol) All potential participants who declined to enrol declined to share reasons for their decision (or were too unwell to approach), therefore it is not known whether it was because they were not willing to be randomised, they were not interested in intervention, or not interested or wanting to participate in a research trial.	≤10% of participants declined to enrol	N	Utilise current available literature on ways to optimise recruitment. In depth training for physiotherapists and consider a video that is accessible for people with cognitive and communication impairments to ensure standardised approach information, take into consideration thoughts and feelings about the Participant Information Sheets for participants from participants, relatives and physiotherapists.
Acceptability of the intervention	15.6% of withdrawals (n=7 during the 3-week physiotherapy period, n=5 in the intervention group, n=2 in the control group)	≤20% of randomised participants withdrew	Y	
Determining usual physiotherapy	In the control group, functional tasks were the most commonly	0% intervention group (e.g. ≥5 sessions per week, ≥8	Y	

	implemented treatment activity, and supported standing was the most frequently adopted position. A breakdown of time spent on these variables were not captured, therefore, it is not possible to know how much the control group differed from the intervention group.	repetitions of sit to stand and standing for 30 minutes) implemented in the control group	
Resources			
Burden	6.0% of the functional standing frame sessions and 4.4% of the control sessions were declined.	≤20% of functional standing frame sessions declined	Y
		≤20% of recruited	N
	12 participants (54.5%) participants declined one or more sessions.	participants declined functional standing frame sessions	Y
	0% follow-up assessments declined in both groups	≤20% of recruited participants declined follow-up assessments	
Management			
Fidelity	Three Stroke Rehabilitation Units had fidelity checking from an independent observer. Site 1: one control group and one intervention group session;	≥3 out of the four Stroke Rehabilitation Units observed	Y
	Site 3: one control group and intervention group session; Site 4: one control group session. There was no fidelity checking at Site 2 because this process was not implemented until after they had ceased recruiting.		N
			N

	Five sessions in total were observed at three sites. Three sessions were delivered as per protocol One functional standing frame session was not delivered as intended.			
Participant adherence in the intervention group	0% completed ≥5 sessions per week in each of the three weeks and 30 minutes standing and ≥8 sit to stand repetitions in each session. 0% completed ≥15 sessions in total over the three weeks and 30 minutes standing and ≥8 sit to stand repetitions in each session.	≥50% unable to undertake the intervention, e.g. ≥5 sessions per week or ≥15 sessions over 3-weeks.	N	Address treating physiotherapist adherence. Provide in depth training, half day on the trial processes and whole day on delivering the intervention to people with severe stroke, incorporating the participants' perspectives. Implement a graded increment of 30% or repetitions of sit to stand and consider a weekly graded approach for both standing duration and sit to stand repetitions and provide definition of sit to stand.
		Standing time in minutes increased 30% in each session up to 30 minutes	N	
	0% participants completed 30 minutes of standing in ≥5sessions in all three weeks 0% completed ≥8 sit to stand repetitions in ≥5 sessions in all three weeks	≥8 repetitions of sit to stand	N	
Participant experience of the intervention	91.0% of sessions were enjoyed 91.0% of sessions required effort			

	93.0% of sessions participants experienced fatigue 66.5% sessions participants did not experience any aches or pains		
Orthostatic hypotension protocol	Orthostatic hypotension was experienced in 8.3% of the intervention group sessions 7.2% of sessions were not completed due to OH	≥50% of participants with OH unable to undertake the intervention	Y
Safety			
During 3-week physiotherapy period	n=26 AEs (16 in the intervention group and 10 in control group) and n=2 SAEs, both in the intervention group 0% unexpected or related to trial	0% AE*; 0% SAE*	Y
	0% unexpected or related to intervention	0% AE*; 0% SAE*	Y
During follow-up visits	n=92 AEs and n=26 SAEs 0% unexpected or related to trial		

* unexpected and related specifically to the functional standing frame intervention. Baseline (T1), post 3-week intervention (T2), 15 weeks post-randomisation (T3), 29 weeks post-randomisation (T4) and 55 weeks post-randomisation (T5).

Table 4.23 Feasibility objectives

Progression to a full trial is based on the criteria set out in the Statistical Analysis Plan, which stipulated that if any one of these criteria meets scenario 3 the trial would not progress in its current design. Table 4.24 shows that the recruitment target and percentage of participants completing their follow-up assessments at 29 and 55 weeks met criteria for scenario 1. However, no

participants completed at least 5 sessions per week and within those five sessions completed the required standing time and sit to stand repetitions, therefore, the trial will not progress in its current design.

	Criteria	Scenario 1	Scenario 2	Scenario 3	Outcome
1	% of recruitment target achieved (50 participants)	≥70% of the target figure	51-69% of the target figure	≤50% of the target figure	90% recruitment target achieved. This criterion meets scenario 1
2	Target figure = 75% of the percentage of participants randomised to the intervention group who participated in at least five sessions per week of the intervention (e.g. 30 minutes of standing, or a 30% increase in standing time every session, and 8-12 sit to stand repetitions). This includes an estimated dropout rate of 25% due to mortality[308,309]	≥70% of the target figure	51-69% of the target figure	≤50% of the target figure	0% participants randomised to the intervention group participated in at least five sessions per week and within those five sessions completed the required standing time and sit to stand repetitions. This criterion meets scenario 3.
3	Target figure = 60% of the percentage of participants randomised who completed their 29- and 55-weeks post-randomisation follow-up assessment. This includes an estimated 40% drop out rate due to mortality[308,309].	≥70% of the target figure	51-69% of the target figure	≤50% of the target figure	60% (27 participants) completed their 29- and 55-week follow-up assessment which equates to 100% of the criteria target. This criterion meets scenario 1.
Proposed action		**Proceed to submitting plan to funder for full trial**	**Discuss with TSC and funder about progression**	**No progression to a full trial in the current design**	**The trial will not progress without addressing adherence**

Table 4.24 Criteria for progression to full trial

Chapter 5 qualitative results

5.1 Introduction to qualitative results

This chapter presents the interview and focus group data that explored the experiences of participants, relatives and physiotherapists involved in the trial to determine whether the intervention and trial processes were feasible and acceptable.

5.2 Aim of qualitative component

The aim of the qualitative component was to explore the experience of using the functional standing frame programme and engaging in associated trial processes from the perspectives of the person with stroke, their relative and physiotherapists. The purpose was to identify challenges that may be overcome and ways of resolving and improving them to maximise success of a subsequent definitive trial.

5.3 Objectives of qualitative component

The objectives of the qualitative component were to explore:

- Means by which the trial procedures (timing and mode of participant recruitment, information provision, methods of data collection for example timing and choice of outcome measures) can be refined to maximise recruitment, retention and acceptability in a definitive trial
- Participants' experiences of engaging in the functional standing frame programme
- Participants' experiences of being randomised, and reasons for, and experiences of, withdrawing from the trial

- Relatives' influence in participants' decision to consent to participate, remain in the trial or act as consultee for their relative
- Physiotherapists' attitudes, thoughts and feelings of implementing the intervention and trial processes and whether they perceive a subsequent RCT to be achievable.

5.4 Data collection

Interviews:

Twenty face-to-face semi-structured interviews were conducted, involving ten patient participants (four who had been allocated to the intervention group), four relatives (one whose relative was allocated to the intervention group) and six physiotherapists were interviewed.

It was intended to interview an equal number of participants in the intervention and control groups, however, due to the number of participants with severe communication impairments or whom were medically unwell, interviews for the intervention group were limited.

It was not possible to interview participants who withdrew from the intervention. Three participants personally made the decision to withdraw, all of whom died shortly afterwards. Three participants were withdrawn by a healthcare professional because they were receiving end of life care, therefore, it was not appropriate to offer interviews. Four out of five of the participants who were withdrawn during the intervention period were in the intervention group.

All patient participant and relative interviews were conducted in their preferred location, e.g. in a SRU either at their bedside behind curtains or in a quiet private room off the ward. Patient participants were present during relative interviews, which was their preference. All physiotherapist interviews except

one were conducted in a private room at their hospital base. One interview was conducted in a hotel close to one hospital base.

Focus group:

Five physiotherapists, (two of whom had participated in individual interview approximately three months after recruitment commenced at their site) participated in the focus group. The focus group was conducted five weeks after recruitment closed, in a non-clinical building in a location central to all sites attending. Three of the four sites were represented at the focus group. One site was unable to join the focus due to long-term significant staff shortages.

5.5 Participant characteristics

Patient participant names and trial numbers, and relatives' and physiotherapists' names have been replaced with a participant identifier to ensure confidentiality is maintained because they could be identifiable to treating therapists. A detailed description of each physiotherapist and their banding is not provided as those familiar with the trial and sites would easily be able to identify each physiotherapist by this description.

Patient participants' age ranged from 51-96 years, all but two were over 65 years of age and retired. Most had communication impairments that affected their ability to express themselves or understand abstract questions. Some patient participants had cognitive impairments, two of whom were unable to recall any aspects of the trial or being involved in it. Some patient participants used few words in response to questions due to cognitive and communication impairments. This resulted in short extracts of textual data. Table 4.25 provides patient participants' characteristics.

Participant Identifier	Gender	Age in years	Communication and/or cognitive impairments	Group allocation
PC1	Female	71	Cognitive	Control
PC2	Male	60	Communication	Control
PC3	Male	65	Communication	Control
PC4	Female	74	Cognitive	Control
PC5	Female	79	Communication	Control
PC6	Male	89	None	Control
PI1	Male	96	Cognitive	Intervention
PI2	Male	51	Communication and cognitive	Intervention
PI3	Male	68	Communication	Intervention
PI4	Female	84	Communication	Intervention

Table 4.25 Patient participants' characteristics

All but one physiotherapist, and all but one relative was female. The four relatives are identified as R1, R2, R3 and R4. Physiotherapists are identified as Physio 1, Physio 2, Physio 3, Physio 4, Physio 5, Physio 6, Physio 7, Physio 8 and Physio 9. Data from the focus group are indicated with an additional FG beside the identifier.

5.6 Themes

Four main themes were derived from the data, reflecting the underlying objectives of the trial: 1) Organisational/cultural factors that impacted on the implementation of the trial; 2) Impact of stroke on participation in the trial; 3) Experience of trial procedures; 4) Patients, relatives and physiotherapists experience of the functional standing frame intervention (Figure 5.1). Data from patients and relatives have been separated out from physiotherapists in each theme with an overarching synthesis.

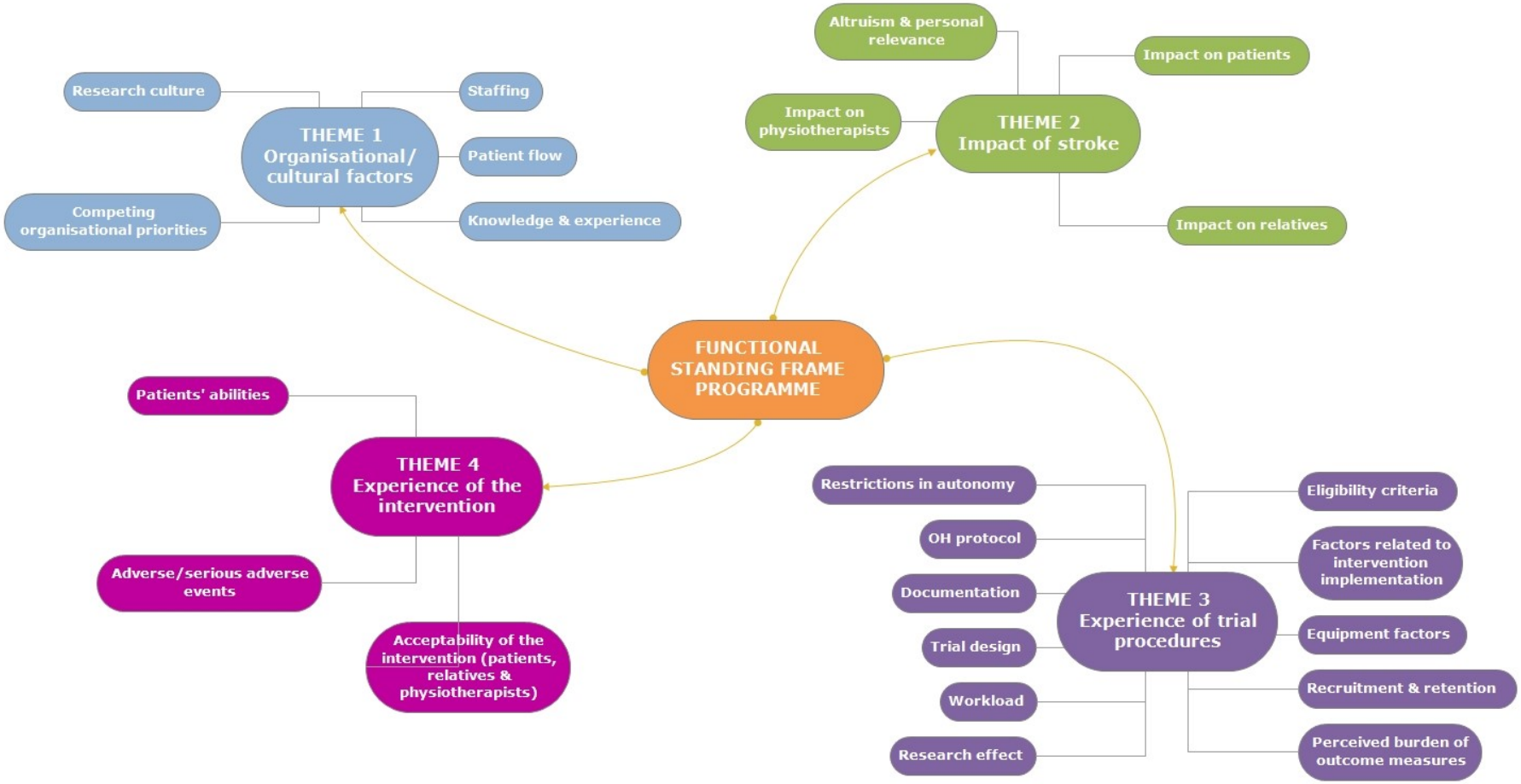


Figure 5.1 Diagrammatical representation of themes

Theme 1) Organisational/cultural factors which impacted on the implementation of the trial

Organisational and cultural factors have the potential to influence the delivery of clinical trials and can impact on intervention implementation, recruitment and retention[352]. Data for this theme is from physiotherapists only.

Staffing

A common finding across all sites was that inadequate staffing levels due to annual and maternity leave, sickness, and new and inexperienced staff made it difficult to consistently screen, consent and implement the functional standing frame programme.

> *"I've had a lot of annual leave in the last two months. It's not helped by B5 going off sick" [Physio 5]*
>
> *"We've only had one physiotherapy assistant for the last few months because we've had someone off sick" [Physio 8FG]*
>
> *"It has all been a bit haywire recently as everyone has been off" [Physio 2]*

Several physiotherapists reported that the focus of rehabilitation has changed with a greater emphasis on rehabilitation being delivered in the community. They commented that this results in a more rapid flow of patients, with a common view expressed among the physiotherapists that the pressure of early discharge results in rehabilitation focusing on drivers for discharge (e.g. ability to perform a safe bed-to-chair transfer and provision of specialist seating) and that intensive rehabilitation was a lower priority.

> *"Thinking about how rehab has changed, the direction that our Trust has been moving is that the majority of the rehab now is being delivered at home because people are going home so much earlier." […] it's trying to get this message across about intensity of practice across really […] certainly with the unit we're on as well, there is so much going on, we find that once people get home, that's where the rehab takes off. The only other thing that might have affected intensity of practice, […] the other*

people who were treating patients were quite new and covering maternity posts, quite inexperienced." [Physio 1]

"Here you're under constant pressure to get people out, so you need to adapt and change their treatment in order to get them home, get them mobile and get them on their feet and safe for discharge." [Physio 7 FG]

The implementation of the functional standing frame programme will vary depending on how severely impaired patients are, but commonly it relies on the availability of two staff members per patient. Some physiotherapists reported they needed three staff members, and this affected whether the standing frame intervention was used:

"We tend to see most people as doubles because that's our staffing allows […] so if we can get them in a standing frame with two people, we will. It's unlikely that we'll have time every day for three people, so if you can't get them in with two, then they're probably going to be tilt tabled or sat." [Physio 2]

Patient flow

Patient flow across the stroke pathway impacted on how quickly potential participants were transferred from acute stroke units to rehabilitation units. This affected recruitment as the more acute patients were screened and excluded because they were deemed medically unwell for rehabilitation:

"We had some people like that who were pushed through to us so quickly, literally one or two days post-stroke. They're not having any therapy because they're so acute, so fatigued and we just need to let them wake up a little bit" [Physio 5]

"Some patients will come straight through to the rehab unit and they would have their stroke like on the Saturday and then in that really acute stage of their stroke […] so, they're with us within 48 hours of their stroke, so they are at a very different stage to others." [Physio 8 FG]

In response to this, two months into recruitment, the screening section in the protocol was amended from "Within 48 hours of admission (or as soon as practicably possible)" to "Within 48 hours of being medically well for

rehabilitation" to accommodate this organisational process and optimise recruitment.

Competing organisational priorities

Several physiotherapists identified that trial procedures competed with organisational priorities, such as pressure to discharge and the routine clinical assessments on admission. The trial protocol required physiotherapists to screen and approach new patients within 48 hours of their admission to the stroke unit or within 48 hours of being medically well for rehabilitation:

> *"I'm finding the 48 hours a little bit tricky to fit in, doing our initial assessment, and we do joint seating assessments with the OTs usually and all the paperwork that goes with that, then check the inclusion criteria and then consent the patient. It feels like 72 hours would be better." [Physio 3]*

Data suggested the physiotherapists wanted to do a good job for both the trial and their patients, but this was challenging. It appeared that this was perhaps not feasible within existing caseloads, to manage the requirements of the trial (paperwork and intervention delivery) and equity of care for both trial and non-trial patients:

> *"We've been trying to make it fair across the ward so the participants in SPIRES haven't always been getting five [sessions], whether they're in control or intervention. […] On the days I prioritise SPIRES that may have an impact on my case load and then vice versa the next day to try and get the right balance" [Physio 5]*

During the recruitment period, at one site, the acute and rehabilitation stroke services merged and co-located. As a result of this upheaval, there was a delay in that site opening and recruitment was a lower priority.

> *"In hindsight for us it was a real challenge because we were combining two teams […]. I think it was just to do with the timing of the unit and there was so much going on because we were co-locating it and all of that, it just took over in the end." [Physio 1]*

Research culture and infrastructure

Although physiotherapists are encouraged to deliver evidence-based practice and have an awareness of current relevant research in their field[353,354], involvement in research locally was reported to be uncommon in most of the sites. Some of the physiotherapists remarked that research was not at the forefront of their minds and this appeared to affect how the trial was perceived and accepted by the wider multi-disciplinary team:

> *"I don't think we're necessarily in the culture of research and that's quite difficult […] That whole kind of evidence-based approach isn't thought of that highly, it's quite a sweeping statement, but it's not at the forefront of people's minds." [Physio 5]*

Whilst the findings suggest there is not a strong research culture and infrastructure across all trial sites, involvement in the trial had prompted some physiotherapists to reflect on their current practice:

> *"It has made me think about standing people for longer than I might have done. Made me think about reducing the length of their rest times and thinking about the rep's of standing up a bit more." [Physio 3]*

Implementing the trial required the involvement and commitment of the wider rehabilitation team. Where this was lacking, some physiotherapists commented that they felt unsupported:

> *"We really struggled with team dynamics and perceptions of the trial", stating that some staff "felt very unsupported, not just from team leads but from other members of the team as well." [Physio 5 FG]*

The level of support from the wider rehabilitation team appeared to affect whether eligible participants were screened and approached resulting in selection bias. A suggested potential solution to this was having Clinical Research Network staff or Research Nurses undertake screening and consent:

"If you had someone completely separate to it, like one of the research nurses, it would remove that potential bias from the patients." [Physio 7 FG]

Knowledge and experience

The participants highlighted that in addition to challenges with staffing, competing priorities and lack of research culture impacting on the implementation of the trial, so too did their pre-trial level of knowledge and experience of using the standing frame. Some physiotherapists lacked experience of stroke rehabilitation and the standing frame. Others had previously used the standing frame. Both circumstances appeared to affect their perceptions of the usefulness of the frame and how they treated and progressed their patients. Two sites used the frame more frequently than others, but none were routinely implementing prolonged standing and repetitions of sit to stand with people with severe stroke, though most had previously used the frame for static standing. It was suggested by Physio 1 that physiotherapists who are inexperienced in stroke rehabilitation and using the standing frame may be less likely to progress patients as much as experienced physiotherapists and this may have implications for a subsequent main trial in terms of protocol adherence:

"The other people who were treating patients were quite new and covering maternity posts, were quite inexperienced. But it's also about risk and stuff, like pushing and progressing patients as much as you or the regular band 6 would have done." [Physio 1]

In summary, several organisational/cultural factors impacted on physiotherapists' experience of implementing this feasibility trial. Findings revealed that staffing resources are limited in some stroke units, the pressure for early hospital discharge is ever present, and change or restructuring of services is a constant feature. Nestled within these organisations are

experienced and inexperienced physiotherapists struggling to deliver a protocolised feasibility trial in departments with a limited research culture and infrastructure, whilst maintaining equity of care for all patients. During the interviews and focus group, the physiotherapists did not use evidence to support their clinical reasoning or reported behaviours. Nevertheless, it was apparent that the physiotherapists strived to do their best for both the trial and non-trial patients.

A range of design issues to consider for the main trial have been identified by the data so far: i) staffing; ii) early discharge; iii) protocol 48-hour deadline for screening and approach; iv) availability of physiotherapists (experienced versus inexperienced); and v) building research capacity.

In addition to how organisational and cultural factors impacted on the implementation of the feasibility trial, how patients experienced their stroke appeared to shape their perceptions of the functional standing frame programme and trial processes, and the reactions of their relatives and physiotherapists. The next theme provides insight into the impact of stroke on patients, their relatives and physiotherapists.

Theme 2) Impact of stroke on participation in the trial

The challenges of conducting clinical trials with people with acute and sub-acute stroke are widely acknowledged. Orthostatic hypotension may interfere with or limit rehabilitation (Chapter 2). Additionally, cognitive and communication impairments may affect potential participants' ability to provide informed consent and understand the intervention, and physical and emotional factors may affect their ability and willingness to participate[355].

Patients' and relatives' perspectives

All patients spoke candidly about the impact of their stroke. Some participants shared how their stroke had raised questions about their mortality, and many reported changes in cognition, speech, continence, vision, sensation, and experienced new symptoms such as fatigue, anxiety and fear.

> *"I'll be honest I didn't know if I was going to be alive in three weeks' time. I felt so bad that I thought I might die" [PC3]*
>
> *"It's like oh I've been hit by a freight train […] difficult concentrating and my short-term memory is pretty much non-existent […] it's affecting my left eye really badly." [PI2]*
>
> *"To me this has been worse than my major heart attack and bowel cancer because this stroke is not a quick recovery […] the fact that I've got no control over my continence is devastating. It's awful, I have never known anything like this." [PI3]*
>
> *"But I could barely talk when they came to talk to me about it. But okay, I was able to take it all in." [PC3]*

Patients acknowledged they were fatigued and developed strategies for managing fatigue. Patients typically recounted that it was important to "push" themselves through the fatigue associated with the stroke and functional standing frame programme. They built-in frequent rests before pushing on:

> *"It was energy zapping, mentally and physically […] I've been able to cope even though I've been tired" [PI2]*
>
> *"Even though I was tired, I pushed myself through it" [PI3]*

Despite physical and mental fatigue, patients and relatives said that people should still be asked to be involved in the trial:

> *"If you're of a low mood anything that distracts you or makes you think that you're going to get better is going to be good for you.* […] *I'm afraid that comes with it. I think as long as you understand that comes with it, as long as you don't think it's personal to you as long as you've been told you're going to feel absolutely shattered, then yes." [R3]*
>
> *"You definitely should be offered to be up and moving. If I had a stroke I'd probably just lie there and feel sorry for myself, so you need to be*

encouraged and motivated. Even if you're fatigued, you should be encouraged to get moving" [R2]

Despite the devastating and life changing impact of their stroke, all patients had hopes of recovery and the future:

"Get back to normal. Just get back to normal. I've always been independent, I've never asked anyone for anything. I just wanted to get back to normal" [PI3]

"Be able to keep myself upright as long as possible to help […] when I got home and being able to walk the dog" [PI2]

"Go where I want to go and do what I want to do. Just a normal life, not to be confined to a ruddy bed all the time" [PI1]

Relatives also described the impact on themselves of their loved one having had a stroke. Relatives spoke about how their lives had been turned upside down, and how relational and household activities and responsibilities had changed:

"… so much else going on not really stroke related stuff. The stress of him having the stroke, not having a job, having to find our rent and probably not really stroke related stuff, outside stuff." [R2]

"It's still a strain getting all my meals, and everything done and I'm just in the middle sort of thing. She used to do everything and now I've got to do it all." [R1]

Whilst early discharge is an organisational priority, impending return home also had an impact:

"I've had to do quite a bit now. I've had to alter the house quite a bit because she's going to be downstairs and she can't make the stairs. I'm wondering now if there's enough room for the carers, but I won't know that until I get the bed". [R1]

Family members were occasionally worried about their relative being in the trial because of their recent and severe stroke, thinking they had been admitted for recuperation, not rehabilitation. However, they still provided consultee declaration:

"I asked my sons as well and we all agreed for her to do that. We know that we can pull out at any time. As long as she isn't over stressed or anything like that." [R1]

Altruism and personal relevance

Despite the devastating and life changing impact of stroke participants were willing to enrol in the trial, and the most common reasons for enrolling were altruistic:

"It might put somebody on the right road again" [PI4]

"[…] just hope I help somebody else" [PC5]

"Because I think it helps everybody … it helps, not me, but other people … I want to help." [PC1]

Whilst patients mostly hoped the trial would benefit others, some hoped they would benefit personally:

"You might get better. But I want to stand on my own, that's a big one" [PC4]

"Strengthen my legs" [PI2]

Relatives hoped their relative would find the intervention advantageous and interesting:

"Anything that we consider an advantage to her and other people later on […] I want her to get as mobile as she can before she comes home." [R1]

"Well I just thought he might find it interesting" [R2]

Physiotherapists' perspectives

Post-stroke fatigue was also acknowledged by physiotherapists who reported that it prevented or limited implementing the functional standing frame programme. Physiotherapists reported that patients were "exhausted" after the functional standing frame programme sessions, which impacted on their ability to practice other activities pertinent for discharge:

"They were so exhausted trying to get them up into standing and their BP dropping, they were too tired to do anything else like working on sitting and functional bed mobility." [Physio 1]

"They couldn't tolerate it, but they could have but then they would have been exhausted for the next professional that sees them and if I did that every day, they'd hate me." [Physio 6]

Other physiotherapists shared strategies they had implemented to manage fatigue such as timetabling and increased communication and co-ordination with other members of the multi-disciplinary team.

"I've tried timetabling. And I'm slowly getting the OTs on board in terms of coming in on a standing frame session, because they had quite a negative feeling towards the study initially, and I've been gently, gently progressing, getting them to come along and creating a place for them within it and reassuring them that there are things within the session they can do" [Physio 5]

Some physiotherapists commented that the severity of stroke affected their ability to deliver the functional standing frame programme:

"We had a couple with really really poor midline, really poor head control and it was taking at least four of us to be getting them into the standing frame and they weren't necessarily enjoying it because they felt so scared. Sometimes it felt too early" [Physio 5 FG]

Some physiotherapist also felt that non-physical consequences of stroke impacted on patients' ability to participate in the functional standing frame programme:

"We've had one or two that because of their cognition and anxiety have struggled" [Physio 4]

Conversely, one physiotherapist reported that the standing frame was more successful than the usual physiotherapy activities she had implemented with a patient with cognitive impairment:

"We were standing him in the standing frame and we had a lot of success in the frame […] to try and work with him in sitting was very difficult because he had a lot of cognitive and language difficulties, it was very difficult to engage him in activities in sitting. You know it was very difficult

almost to find that way in. But by getting him up in standing we found that we had more success." [Physio 7 FG]

Several physiotherapists spoke about the unstable nature of stroke and identified that patients have complex needs, commenting that the complexity of a patient's condition sometimes affected whether they were able to fully participate in the three-week intervention period:

"A couple of mine have been consented and then not actually been able to commence their therapy for quite a good chunk of the three weeks because of being medically unwell or actually having to go away from here to the acute hospital". [Physio 4]

In summary, these findings reveal that stroke is devastating and can turn both the patient's and their relative's lives upside down; for some there is a sense of impending death. Both parties are trying to understand and come to terms with life after stroke, dealing with the physical and emotional consequences as well as social, occupational and financial issues that can arise. All these issues have the potential to affect recruitment and retention in clinical trials. Despite this, participants were still willing to take part in the trial and continue with the intervention. Hopes of recovery and being able to return to their previous functional abilities, and altruism, were predominant factors in influencing recruitment and retention. Relatives were profoundly affected by their loved one having had a stroke, describing many emotional and practical consequences they were having to deal with, within the context of an uncertain future. Despite this, they were willing to act as consultee and support their loved one through the trial. There were differing beliefs and opinions of physiotherapists as to whether the standing frame was an intervention suitable for people with severe stroke, and this appeared to affect the way the intervention was delivered within the trial.

The impact of stroke on both patients and their family is evident in the data. Surprisingly physiotherapist's perception of the impact of stroke and using the standing frame with patients were often at odds with patients themselves. Whilst physiotherapists reported patients were "too tired" or "couldn't tolerate it" patients described themselves as able to cope and "push through the tiredness". Both patients and their relatives emphasised that despite this devastating and life changing event, patients should still be offered the opportunity to be involved in the trial. In practice however, physiotherapists were the gatekeepers as to whether or not the standing frame was incorporated into the rehabilitation programme, on the basis of their clinical judgment.

This theme highlights the profound impact of stroke, affecting patients, their relatives and physiotherapists in diverse ways. The following theme captures experiences of the trial procedures from all three perspectives.

Theme 3) Experience of trial procedures

Understanding experience of trial processes and procedures is an important part of feasibility testing as these data can be used to improve trial procedures to maximise the chance of any future trial being successful[356].

Physiotherapists' perspectives

Eligibility criteria

Eligibility criteria was a contentious topic among physiotherapists in both the individual interviews and focus group. Opinions about the eligibility criteria were varied and perceived as "ideal" or "too broad":

> *"You don't need to worry about the severe ones, they need to go through this" [Physio 6]*
>
> *"I think that it's more ideal for those type of patients anyway [severe or very severe stroke] if it' wasn't randomised and we could choose, we'd*

probably choose the more the 5 [mRS score], heavier severe strokes to be in it if it was left to us to decide." [Physio 3]

"I think it's just too broad. So, the majority, the vast majority of our patients are a 4 [mRS score] and so then, they're a 4 so on the surface they look like they're eligible for the trial, but actually they're mobile with one or mobile with supervision, they're not quite reaching that 3 category, but then functionally too good for the standing frame." [Physio 5]

There was disagreement among physiotherapists about which patients were best suited to the functional standing frame programme in terms of (dis)ability. However, several physiotherapists acknowledged that no physiotherapy intervention is suitable for every patient:

"I think people who, you know someone could quite happily stand and transfer with say a Return and one, I'd be thinking they would be a bit too good for the SPIRES trial. So, if someone was doing a transfer like that, they're too good, but maybe they were at the point of using an Encore Stand Aid or a hoist, those are the patients would I would be thinking they are more appropriate for SPIRES as it were." [*Physio 2]*

"And it was the mRS 5, feeling as though, on a day to day basis I probably wouldn't put someone who didn't have sitting balance or head control in a standing frame, let alone for 30 minutes" [Physio 8 FG]

"[…] it's the only option for people with severe stroke" [Physio 6]

"No physio intervention is going to be suitable for everyone, but for the right patients I think it's a useful and beneficial adjunct." [Physio 5]

The mRS is used to classify severity of stroke, and participants were eligible to join the trial if they were mRS 4 (moderately severe) or 5 (very severe). It was unanimously perceived by physiotherapists as open to interpretation. Some physiotherapists reported it is not representative of current clinical practice because no patient is "bedridden" (mRS score of 5, very severe) due to current early mobilisation practices. Some physiotherapists deemed patients bedridden if they were unable to sit out for 2-3 hours because this would prevent them from being discharged home with a package of care. This caused "moral dilemmas" (Physio 6) for physiotherapists as to how to score patients and who to approach for consent. Several physiotherapists shared their thoughts about

alternative measures that they deemed more appropriate to use instead of the mRS:

> *"I'm thinking of something like the FIM FAM [Functional Independence Measure and Functional Assessment Measure]" [PhysioFG9]*
>
> *"It's their functional ability isn't it. I don't know if the PASS [Postural Assessment Scale for Stroke] may be?" [Physio 8 FG]*
>
> *"Maybe the Modified Rivermead which is quite functional again" [Physio FG7]*
>
> *"I think you're better off going with impairments and activities, rather than an outcome measure that is not clear" [Physio 6]*

Several physiotherapists agreed that sitting balance would be an appropriate criterion for determining eligibility, but there was no consensus:

> *"Maybe something a bit more functional that reflects a little bit more about their mobility and their sitting balance and standing, might wheedle it down a little bit." [Physio 7 FG]*
>
> *"I think some trunk control to be able to sustain some sitting balance, not necessarily be able to sit for half an hour, but just to be able to have something" [Physio 8 FG]*
>
> *"So, I don't think there's enough evidence that you need to be able to have independent sitting balance before you try and stand up in a standing frame" [Physio 6]*

Factors related to implementing the functional standing frame programme

Several physiotherapists reported that stroke severity influenced their ability to deliver the functional standing frame intervention with people with very severe stroke. They highlighted that people with more severe stroke required more physiotherapists, which challenged resources:

> *"The only negative things with it really is that you need quite a lot of hands; sometimes three or four people so it's obviously just taking other therapists off the ward but that's the only negative thing about it." [Physio 4]*
>
> *"It is quite resource demanding" [Physio 5]*

The duration of the functional standing frame programme was three weeks, however, opinions varied among physiotherapists about the duration. One physiotherapist commented that three weeks was insufficient and ideally the intervention should continue in the community post-discharge, whereas others said they would prefer the intervention to last two weeks. Some physiotherapists commented that regardless of the duration of the intervention, it would be preferable to have flexibility to allocate time to other activities that they perceived pertinent to discharge:

> *"I think three weeks was a good amount to start with […] so, to say it's three weeks ideally, but actually then you can progress your patient." [Physio 6]*
>
> *"I don't know that three weeks is long enough, but also again because of our length of stay and stuff, a lot of people are obviously going out into the community in that time, so if it could be continued in the community." [Physio 1]*
>
> *"I wonder whether a two-week period […] then you've got a week to do other discharge stuff or you might have a week before they start to do the trial to get midline and start the trial, so two weeks would be flexible." [Physio 9 FG]*
>
> *"I'm just wondering if you could keep it for three weeks but say so many out of five days you did the standing frame, so rather that it be 10 consecutive sessions, could you do 10 days out of the three weeks. Something like that, so in the early days still be, because you might want to do a session with the nursing staff when you're looking at positioning in bed, it could be you a bit of breathing space." [Physio 3 FG]*
>
> *"[…] whether there was any flexibility even it was four sessions for 30 minutes per week, so there was other sessions where you could still do things like bed mobility" [Physio 3]*

The theoretical basis underpinning the choice of a three-week duration of the functional standing frame programme in this trial was based on previous studies to facilitate intensity of practice[95,85]. The intensity of the intervention was acknowledged by only a few physiotherapists:

> *"you're trying to get that intensity aren't you. If you start expanding the time they do 21 sessions, you're not going to get that intensity of practice.*

In an ideal world, you'd do it for longer and you'd continue the intervention in the community." [Physio 1]

All physiotherapists unanimously agreed that 30 minutes was a good amount of time for each functional standing frame intervention session. However, opinions were divided about the 15 minutes of usual physiotherapy:

"15 minutes often was not enough to do all the other things, perhaps their bed mobility, transfers and stuff." [Physio 3 FG]

"Sometimes I'd just think oh god I just want to do this with the patient and then it comes to like the 15 minutes at the end and you'd have to do the practical things like the transfers, the things that are going to get them home because we still only had that length of time with that patient" [Physio 8 FG]

"It is good that you have the 15 minutes of normal physio as well, so you can explore other things relevant to their therapy." [Physio 4]

The protocol stipulated that participants in the intervention group needed to work towards performing eight to 12 repetitions of sit to stand within their 30 minutes in the standing frame. Most physiotherapists agreed that eight to 12 repetitions should be a minimum with no upper limit. However, several physiotherapists acknowledged that not all participants with very severe stroke achieved the recommended number of repetitions, despite adopting a graded approach:

"If you're not using that [electronic lifter component] you can do loads of sit to stands and 12 doesn't seem like very many then. But I think if you're using the electronic component of the standing frame, and you've got a patient who sit to stand is hard for, then maybe you wouldn't." [Physio 3 FG]

"Quite a few never reached the eight" [Physio 5 FG]

Some of the organisational factors such as the 'discharge driven culture' were apparent when physiotherapists discussed the duration of the functional

standing frame programme and the 15 minutes of usual physiotherapy. This was also evident in the next sub-theme, equipment factors.

Equipment factors

Design and brands of standing frames varied across sites. Some sites had Oswestry standing frames[357] that are made mostly of wood, others reported having more "robust" and "sturdy frames" made of metal, some with more advanced technological and mechanical features, such as the THERA-Trainer Balo[358]. Some physiotherapists had access and/or experience with different types of standing frames:

> *"The Oswestry takes a long time to get patients in and out of […] and it's not great from a manual handling perspective" [Physio 5]*
>
> *"I'm not sure it's any easier to get them into the Balo" [Physio 7 FG]*
>
> *"In terms of manual handling it's [Balo] so so much better. And the amount of adjustments you can do: hips height, knee height, table height, move the knee pads individually so in terms of getting the frame to fit the patient that's a benefit as well. […] I would say the Balo is sturdy and more robust … the Oswestry is a bit creaky isn't it and sometimes you'd think oh is this going to hold them up." [Physio 3]*

Some physiotherapists highlighted the standing frame was not transferable to the ward or home environments, and suggested equipment routinely used on the ward for standing transfers (e.g. Ros-Return, MoLift, Arjo Stand Aid etc.) would be more suitable. They remarked that these pieces of equipment would allow greater intensity with more frequent opportunities to stand. Some physiotherapists stated that if a patient's goals were to be using a specific piece of equipment for discharge, they should be using this in their therapy sessions instead of the standing frame. They also commented that using different pieces of equipment would enable patients to see themselves progressing:

> *"[…] I worry slightly that the patients perceive that I'm still using the same piece of equipment that I was three weeks ago, even though we know*

we've made it a lot more challenging […] sometimes that can be hard for the patients necessarily to perceive progress." [Physio 7 FG]

"We've had some patients that had been using the standing frame, but they would be using the Ros Return on the ward, so it's a more challenging bit of equipment outside of their therapy. So being able to use different bits of equipment would be better." [Physio 8 FG]

Some physiotherapists reported feeling the standing frame intervention created false hopes for progression in patients with very severe stroke who were standing in the frame but required a hoist for transfers on the ward and for discharge. This led to difficult conversations with patients and families:

"[…] the family perceived it was a good thing that they were up and standing and in the standing frame, but that wasn't transferable because they weren't able to use other bits of equipment for discharge. So, they had that perception that oh good my family member is standing and able to stand, but we felt that they weren't progressing." [Physio FG9]

A couple of physiotherapists reported that patients were concerned with how the standing frame looked:

"It's a bit daunting isn't it, seeing that in the corner of the room a little bit" [Physio 4]

"I think it can be quite scary for patients, so I think it can be quite daunting, there are lots of straps and poles, so I think it depends patient to patient as to whether it is an enjoyable experience for them and the benefits of using it." [Physio 5]

Foot sensors were supplied for all sites to enable physiotherapists to monitor the patient's weight distribution during standing. There were several iterations of the foot sensors following feedback from some physiotherapists. All physiotherapists reported that the foot sensors were unreliable and temperamental, and this made delivering the intervention more difficult:

"[…] they were quite temperamental, and they had to be exactly in the right place, that added just another element of we were not getting our hands on our patients and not keeping them in alignment and midline […]. Even with three of us in there, it was just difficult to get feet on the scales

in the right place, check the sensors, keep them going back to check the sensors" [Physio 5]

"I'm not sure that the patients we used them with particularly liked them either. Because I think they were like well why am I not putting my feet on the floor?, why am I putting them on these funny block things?, I think that kind of triggers some anxiety with patients as well. There were a couple that were cognitively intact and pretty good and understood the explanation, but patients with either language or cognitive or perceptual difficulties, it was again putting their feet on the scales was abstract well why am I standing on those anyway, let alone moving their weight around." [Physio 5 FG]

"We haven't had much luck with the foot sensors" [Physio 3]

The foot sensors were provided to enable physiotherapists to monitor and facilitate postural adjustments. They were based on the recommendations of a systematic review to improve monitoring of standing in a standing frame. However, some physiotherapists emphasised that foot sensors would not necessarily facilitate a positive outcome:

"The problem is if they see that all their weight is all this side they do all sorts of things to try and get their weight across, so it doesn't always work even if they get that feedback it doesn't always get the best outcome for them, so sometimes us visualising it is better." [Physio 3 FG]

"It wasn't terribly successful, because similarly it's very abstract for our patients sometimes and I've had much more success with either visual vertical like a line in the curtain or a line on the window or facilitation" [Physio 7 FG]

Some physiotherapists expressed a preference to use their own clinical judgement when evaluating weight bearing in the frame instead of the foot sensors, stating "as an experienced therapist that's what we're looking for" (Physio 5):

"We used clinical judgement. As physios that's what we look for; where is their midline, is their weight going through that leg or are they just hitching off the other one and you can clinically, and yes okay it might not be as accurate as they've got 50kg on this one and 60kg on that one, but you are looking to facilitate for them to take weight on to their affected side and get activity that side." [Physio 5]

Recruitment and retention

Some physiotherapists reported to being selective about which patients they did and did not approach for consent to enrol in the trial which they related to who they perceived as being "too good" (Physio 5) or "too impaired" (Physio 2) or who would not cope with the functional standing frame intervention:

> *"Not that we did much cherry picking, but if you had someone else coming in it would take away our clinical judgement as to whether somebody was suitable may be." [Physio 3]*
>
> *"I wouldn't say we picked and chose loads, there was only one lady really that I can remember thinking actually she does meet the criteria, but it wouldn't be right, and we did record that we'd made that decision, so it's in the log"* [Physio 3 FG]

A few physiotherapists at one site reported there were patients who met the eligibility criteria, but they were not approached, stating:

> *"As a team I think if there was that better scope of person to be within it, maybe we wouldn't be feeling so much that we don't want to put them in". [Physio 2]*

Some physiotherapists appeared to be protective of their patients, potentially adopting a paternalistic role which affected their decision to approach eligible patients. Paternalism in clinical trials is acknowledged as a negative factor in recruiting to stroke clinical trials[359]. Several physiotherapists said that many patients should be using the standing frame "earlier and more", however, some revealed that they did not screen or approach patients if they felt the patient "couldn't tolerate" or "cope" with the intervention:

> *"I think people are quite protective yeah, and I think there are probably quite a lot of other people who should be using the standing frame earlier and more." [Physio 1]*
>
> *"I think there was an element that, oh we don't have time to consent this patient and also, it's probably quite a good thing that we didn't put them on to the trial, because actually if they go into the standing frame I don't think they would cope." [Physio 8 FG]*

Most physiotherapists interviewed agreed they would prefer a dedicated person (not one of the treating physiotherapists) to screen and consent potential participants, e.g. Research and Development or Clinical Research Network staff to minimise coercion, selection bias and alleviate physiotherapists having to spend time on the consent process and completed associated paperwork:

> *"It would also take away from any conflict on the ward if someone external was coming in to consent, it would take away that pressure on us" [Physio 5 FG]*
>
> *"[…] the consenting does take time" [Physio 3]*
>
> *"I do worry that the patients might think well the physio is coming to talk to you about a physio related study that if they don't say yes, they maybe damage their relationship with you already. You know the physio thinks I should do it, so I should do it." [Physio 7 FG]*

Physiotherapists reported to feeling more comfortable involving family in the consent process, even when patients were able to provide consent themselves:

> *"Slightly for my own piece of mind as well. I was talking to families and giving them the information, even if they weren't going to be the consultee consenting and I was consenting the patient, just so they were fully aware of what their relative had given consent for" [Physio 7 FG]*

Perceived burden of outcome measures

One physiotherapist undertook the role of blinded outcome assessor for all participants recruited at their site. They shared their experience of conducting the patient-report outcome measures and what effect it had on them personally as well how they perceived it affected the patient:

> *"We use the PHQ-9 regularly on our unit as a screening tool for all patients, unless they've got aphasia, but when I'm actually having to do it, I was like blimey, these are really challenging things to do with people when you've not built up a rapport with them […] One of the patients did start getting very tearful about it and it was a bit uncomfortable and you just feel like you're going in a bit cold really" [Physio 1]*
>
> *"I felt stupid asking these questions, you know it's obvious you're not able to do a lot of these things" [Physio 1]*

The blinded assessor reported finding the patient report outcome measures challenging with people with communication difficulties and fatigue:

> *"Quite a lot of them had communication difficulties, which made using the outcome measures very challenging" [Physio 1]*
>
> *"I think with the nature that people we were recruiting, the length of the outcome measures they were getting very fatigued, I found that it was really hard, well I couldn't' do it all in one sitting really, and a lot of the questions. I mean it's fine because things like the Barthel and the Edmans you can fill in on their behalf or from a clinician." [Physio 1]*

The blinded assessor also said they felt the phrasing of some of the questions in the patient report outcome measures were not positive:

> *"Well I feel it's not very positive. It draws attention to what's hard, difficult, what can't you do" [Physio 1]*

The SAQoL-39 was perceived as having too many questions, many of which were not appropriate for people with severe stroke:

> *"No, it's way too much. But also, well I guess, I'm just thinking about the people we recruited, but they're never going to achieve half of these things on here. So, it almost seems to be pitched at a very high level." [Physio 1]*

The blinded assessor commented the proposed physical secondary outcome measures were "straight forward" and did not identify or report any problems implementing these measures.

Research effect

Physiotherapists emphasised that being involved in the trial was "novel and exciting" and facilitated awareness of a different evidence-base that can improve clinical practice and "a really good way of evaluating your practice and challenging your practice and thinking" (Physio 7 FG). Most physiotherapists reported that they will be using the standing frame more often in their clinical practice and standing their patients for longer, reducing rest times, increasing repetitions and encouraging more dynamic movements:

"My practice has changed that I would think oh yeah they might be quite good in the standing frame and you wouldn't necessarily do 30 minutes five days a week for three weeks, but actually it's kind of thinking about yes that might be quite good for that person.[…] being involved in research is quite novel and exciting hopefully that will inspire to be, at least be more aware of different evidence base and looking at how that can improve our practice" [Physio 5]

"I think it has made me think about standing people for longer than I might have done. […] It has made me think about, may be reducing the length of their rest times in between to try and get longer times standing, I think it has maybe pushed me a little bit more to get them on their feet for longer in the session […] I think it has made me think about the repetitions. I think I was very guilty before, using the standing frame a fair amount but getting people up in it and they would then just be up in it." [Physio 3]

One physiotherapist commented that being involved in the trial had opened a "can of worms" for physiotherapists:

"The real can of worms that you've opened is, you're asking to justify why their patients aren't standing for half an hour every day." [Physio 6]

One physiotherapist reported that the trial facilitated them to evaluate the outcome measures used in their stroke unit:

"It has made us look at what screening tools we use in depression, because I'm like I don't know this is the best one [PHQ-9] that we should be using with people, especially when the throughput is so quick. […] It's also made me think as well, how do we access standing frames in the community for the more severely affected stroke patients." [Physio 1]

Workload

All physiotherapists commented on the workload associated with the trial. Physiotherapist who were PIs reported unexpected additional workload and responsibilities, specifically around reporting SAEs:

"I am a little bit worried about it because it did take up quite a bit of my time to find out that information, so that was something I wasn't expecting" [Physio 3]

Throughout the trial an additional PI was appointed at two of the sites which PIs said helped share the workload and responsibility. Some PIs remarked that the

rest of the therapy team were unaware of the workload and responsibility involved in being PI, and this had implications for managing their caseload during the trial.

> *"There's not the general understanding of how much work goes into the day to day running of the trial. And that's across the board […] there's a lot behind the scenes. […] I was really worrying about it, it was really stressing me out" [Physio 3]*

PIs at two separate sites developed and implemented a checklist to help keep track of the processes and documentation associated with the trial which treating therapists also said they found helpful:

> *"Having that is really helpful because you sign it and you can see what you've done and if you ask somebody to photocopy something and send it off you can see that it has been done. That has been really useful." [Physio 4]*
>
> *"I find it so easy [to keep track of everything"]" [Physio 2]*

All physiotherapists noted that familiarisation increased their confidence with trial processes. They reported to trial and error in the early stages but made adaptations and felt "au fait" with treating therapists at individual sites establishing a rhythm when delivering the intervention.

> *"By the end we changed how we did quite a lot of things whereas at the beginning we were like, we'll try like this and see how it goes. But adapted along the way." [Physio 9 FG]*
>
> *"We're definitely becoming more 'au fait' with using that particular standing frame and being able to problem solve how we look after an upper limb. Everyone now sort of has their place if you like" [Physio 5]*

Trial design

Physiotherapists considered that the current trial design was appropriate. They acknowledged a cluster RCT may be easier in terms of blinding, but said they felt that having both control and intervention groups at each site would have a

number of advantages such as helping to maintain motivation and interest for physiotherapists as well as challenge their practice:

> *"Cluster RCT may be easier in terms of blinding, you just have control or just have the intervention" [Physio 1]*
>
> *"I think that would be really labour intensive […] if you were the intervention site […] I don't think it would be practical without extra staffing. We would need extra help […] if it is completely random to who you're going to get, I think that would help keep the motivation and keep it interesting." [Physio 5 FG]*
>
> *"if you just had the control group I think you'd just bob along and do what you always do and you wouldn't have that challenge to your practice" [Physio 7 FG]*
>
> *"[…] like we've all said we're all doing different things in our control groups and you'd get more of a picture of what a normal physio session would look like if you had different sites, rather than just a couple." [Physio 3 FG]*

Documentation

All physiotherapists commented that there was a lot of paperwork, and the photocopying was time consuming. Most physiotherapists implemented strategies such as delegating photocopying to administrative staff or assistants. Some sites use electronic documentation for patient notes, and they reported that having to scan the CRFs into these systems was time consuming. Several physiotherapists suggested that electronic CRFs would be preferable:

> *"The photocopying was quite onerous" [Physio 3 FG]*
>
> *"I don't know if this is even possible, but I would have found it better to do online […] we kept missing bits out and not filling bits in and if there's some way of having it online so that it prompts you to fill it in, then you wouldn't have all those queries" [Physio 2]*

Physiotherapists were required to capture the content of the 15 minutes of usual physiotherapy sessions for participants in the intervention group, and the content of the control group to enable a description as to what usual physiotherapy was for these people with severe sub-acute stroke. Although physiotherapists recognised that capturing what they did in usual physiotherapy

sessions was a good idea, they highlighted there was nowhere to record how long the patient spent on individual tasks/activities. This led to some concern about what judgements the research team may make about the content of their sessions:

> *"It sounds like I didn't do a lot, I felt I did more, but I don't think it (the CRF) recorded it all" [Physio 2]*

Some physiotherapists commented that the CRF for the intervention group also failed to capture everything they did with participants:

> *"So, the session was 30 minutes but there was only one stand. Well, it kind of looked like, well, what were you doing in between. But actually, there was a huge amount of getting them onto the plinth, getting them set up, getting up in to standing, getting back down on to the plinth and that isn't necessarily captured in the CRF." [Physio 5 FG]*
>
> *"I can imagine someone looking at that and thinking "what were you doing with your patients?". They stood up twice for like 10 seconds and you've said that you'd been with them for 30 minutes […] So, there were patients […] that we couldn't really explain what we did." [Physio 7 FG]*

Physiotherapists appeared to struggle with not being able to write free text to justify what had or had not been done during the sessions. They were notably frustrated that the CRF did not capture all the activities they had been doing with their patients and were concerned that researchers reading the CRFs would pass judgement on them.

There were several versions of PIS: a standard version, a multiple page version for people with mild to moderate aphasia, and a double-sided A4 sheet for people with severe aphasia. All physiotherapists reported preferring and using the PIS's designed for people with aphasia. The multiple page PIS for people with mild to moderate aphasia was the most popular and it was perceived as easier for the patient to understand (even if they did not have aphasia) and

easier for the physiotherapist to talk through. They suggested that patients and families struggled to digest the information in the standard PIS.

> *"The multiple page aphasia friendly participant information sheet is really useful and even if they don't have aphasia. Nicely laid out, easy to read, it's really clear what they're expected to do" [Physio 4]*
>
> *"I don't think I gave anyone the complicated one [standard PIS] even if they were cognitively able […] I think even for those who are quite able it's still an awful lot of information, so I tended to give them the middle one [multiple page PIS]" [Physio 2]*
>
> *"People struggled to digest the standard one [PIS] even families" [Physio 4]*

Some preferred and used the double-sided PIS for people with severe aphasia:

> *"I normally take the double-sided Aphasia friendly one. It's a lot easier to understand […] it's quite a clear, this is actually what that whole document means, broken down into a really simple image. It's a bit easier to look at I think." [Physio 4]*
>
> *"The aphasia friendly one page one has a diagram, it's simple and they can understand" [Physio 5]*

Overall the protocol was reported as being acceptable to all physiotherapists, although they acknowledged it contained a lot of information, but it was easy to refer to. Some physiotherapists acknowledged that they are not as strict in following procedures in clinical practice, but in a research study a protocol is necessary and provided protection for them:

> *"Some of it is getting to know the protocol and at each stage and each session […] Now I know I'm following it and I know it well enough to go ahead with it and now and again I go back to it and check." [Physio 5]*
>
> *"…and the fact is, in clinical practice we don't have a protocol, you have to have a protocol that you follow because I think it protects you." [Physio 6]*

Orthostatic hypotension protocol

Taking manual blood pressures with people with very severe stroke was reported as being challenging for some physiotherapists in terms of the number of staff required to assist participants into standing and take the blood pressure.

It was apparent that they did not consider this as part of their usual clinical practice when standing patients, therefore, had to undergo training to take manual blood pressure as part of this trial. Several physiotherapists commented that they usually judge the presence of OH on symptoms and were surprised that some patients who were asymptomatic had a significant postural drop:

> *"[…] it was taking three or maybe four to get the person up into standing and then have the extra person to take the blood pressure and it felt quite pressured because we wanted to be looking at their alignment and making sure they were safe and checking them and having to do the blood pressure […] So, I think that felt quite fraught quite a lot of the time." [Physio 5 FG]*
>
> *"I think on the blood pressures note, we did them as part of the trial but in clinical practice we wouldn't always do blood pressure checks and that took a lot of time" [Physio 9 FG]*
>
> *"He had orthostatic hypotension and then we were sitting down because we were working with our stroke nurse and she was doing his blood pressure and she said you need to sit this man down and he was pretty much asymptomatic." [Physio 7 FG]*

The comments from Physio 7 FG regarding the asymptomatic patient will be valuable for future training to emphasise the importance of taking blood pressure during standing and optimise adherence to this trial process.

Some patient participants who were diagnosed with OH during trial assessments wore abdominal binders which physiotherapists reported had different effects:

> *"We used quite a few [abdominal binders]. Some successfully, one I can think of not successfully. We used an abdo binder but he was nauseous and it made him feel more nauseous quite claustrophobic, hot and he just didn't' tolerate" [Physio 5 FG]*
>
> *"It has an immediate effect" [Physio 9 FG]*

These comments will be valuable for future training to emphasise the effect of the abdominal binders.

Restrictions in autonomy

Some physiotherapists said the functional standing frame protocol restricted their autonomy in what they could and could not do with their patients in intervention sessions:

> *"I tend to chop and change and be kind of, I'll do a little bit of this and a little bit of that and I couldn't do that and it limited the variety of what I was doing with the patient* […] *if you're constrained to just do standing, I didn't feel that my therapy, my physio sessions could evolve with my patient's needs and changing needs and changing discharge plans." [Physio 7 FG]*

Although the protocol was perceived as restrictive for some physiotherapists, one physiotherapist in the focus group commented that some physiotherapists tend to move on too quickly, which may be detrimental to patients:

> *"[…] because I think sometimes we do move on too quickly" [Physio 5 FG]*

Some sites that regularly used a standing frame as part of their usual physiotherapy prior to the trial perceived the trial as "restrictive" as they interpreted the protocol as stating they were "not allowed" to use the standing frame at all with participants in the control group. However, the protocol stated, "Therapists will be advised not to change their usual physiotherapy practice and start to implement a standing frame programme with participants in the control group if this is not part of their usual physiotherapy practice", which was emphasised in the face to face training.

Whilst some physiotherapists expressed that they struggled with the lack of flexibility and variation in their practice, others highlighted opportunities to be creative:

> *"We did get quite creative with the standing frame, like PADLs in the standing frame […] and that then helped to involve our OT colleagues as well and we'd play games, get the Wii out […] you can make it patient specific which is nice because obviously if it was rigid you wouldn't be able*

to tailor it to your specific patients and that may have been a problem." [Physio 5]

Patients' and relatives' perspectives

Eligibility criteria

Patients and relatives agreed that there should not be an age limit on people joining the trial:

"[…] because some 60-year olds are quite old, and some 80-year olds are young. It makes no difference" [R3]

"No because I think there are some 90-year olds who are very spritely and do need to be included as well" [R4]

"Certainly [is it okay to ask people to join the trial who are a similar age to you?]. I look at it like this. I'm 96, you can't last forever, so you take life as it goes." [PI1]

Patients and relatives agreed that having co-morbidities should not affect people being offered the opportunity to join the trial:

"Everyone deserves a chance" [PI3]

"I don't see any problem as long as they're sort of well enough to do physio, it's all for their benefit. It will probably benefit their other problems as well" [R4]

Factors related to implementing the functional standing frame programme

Opinions varied among physiotherapists about the duration of the intervention sessions. Despite patient participants not having prior experience or knowledge of stroke rehabilitation, they appeared to be accepting of the duration of the functional standing frame sessions:

"I think it's necessary to have enough time to stand. For me personally yes [it was long enough]. I think if you rein it in you're not learning as much as quickly as you should". [PI2]

Equipment

In physiotherapists' perspectives above, a couple of physiotherapists reported that patients were concerns with how the standing frame looked. However, in

contrast, when patients were asked what they thought about how the standing frame looked, they said

> *"No, it didn't look scary, it wasn't scary" [PI2]*
>
> *"I didn't think anything […] didn't think it looked scary" [PI3]*
>
> *"[…] no it wasn't scary" [PI4]*

Most patient participants spoke positively about the standing frame. Some participants in the control group had been using the standing frame and they also shared their thoughts and feelings

> *"No" [Did you ever feel worried using the frame?]. It felt a bit strange, but everything is strange […] it gives you back a little bit of independence." [PI3]*
>
> *"Bewildered isn't the right word, I don't know what the word is […] it wasn't easy, but neither was it difficult." [PI4]*
>
> *"It [standing frame] gives you confidence to do it [stand]. It's a good design because it makes you feel safe, because you're surrounded." [PI3]*
>
> *"You feel like Robocop, like nothing much else can touch me" [PC2]*

All physiotherapists reported that the foot sensors were unreliable and temperamental, and they expressed a preference for using their own clinical judgment. Only one patient was able to recall the foot sensors, reporting they were beneficial. He also shared suggestions for future modification:

> *"The scales need grip underneath them as they tend to slide when you're standing forward, because there's only 4 pedestals as feet on the scales, they slip backwards when you're pushing yourself forward […] would be good in the actual standing frame itself if you had a display on the front panel so you could see where your weight was being displaced" [PI2]*

<u>Recruitment and retention</u>

The protocol stipulated that potential patient participants should be approached within 48 hours of being medically well for rehabilitation (or as soon as practicably possible), which was often within 48 hours of admission. Most patients reported that the timing of approach was acceptable:

"I was pleased about that because you feel like you're moving on. I don't think there's a time when you shouldn't speak about it [research]" [PI2]

"Yes, I think it was the right stage. It might have been a little bit too early for me, but it enabled myself to focus on it. I'm ready for it […] We're all different people, lots going on. I'll be honest I didn't know if I was going to be alive in three weeks' time" [PC3]

Relatives were also accepting of the timing of approach for their loved one:

"I think it's good. I mean you should be, like falling off a horse and getting straight back on it shouldn't you really." [R2]

"…quite soon after, but then I suppose you've got to catch these things in the bud really eh" [R1]

"I think it was about right. We had time to land and settle, and then you get asked" [R3]

Most patients said they had never thought about withdrawing from the trial:

"No, because I'm not a, because I'm not a person who gives up easily. No there was never a thought about stopping" [PI4]

"Sometimes yeah, but only for a split second and I don't dwell on it" [PI3]

All relatives knew that they could withdraw their loved one, but all said that they never considered it:

"We know that we can pull out at any time" [R1]

Relatives who provided consultee declaration said they "didn't mind" being approached and making that decision on behalf of their loved one. Most relatives discussed the decision with other family members:

"I got hold of the boys and we all decided that really we ought to […] everybody decided it was the right decision" [R1]

"I probably wouldn't have been quite so keen if she wasn't willing, but then if she hadn't had been able to make the choice I would have talked to X [R3's brother] and we probably would have said yes anyway." [R3]

<u>Burden of outcome measures</u>

Patients reported they did not mind being asked questions about any aspect of their stroke and how much help they needed, if the questions were useful:

“I don’t find them intrusive, it’s something you need to find out because you need to know how people feel. I don’t have a problem, you really explained, and we went through what you were doing, why you were doing it, it’s all fine, I don’t have a problem with that.” [PC2]

“I don't mind if it's going to help me or somebody else” [PI1]

Trial design

Except for one patient participant, there was a sense of acceptance of group allocation:

“this was my preferred choice” [PC2]

“I was happy to do either” [PC1]

“It doesn’t bother me at all, no” [PC5]

“Don’t mind” [PC3]

One patient in the control group reported feeling that the group he was allocated to suited his needs, stating he would not have wanted to be in the intervention group. Conversely, a participant who was allocated to the intervention group shared how he would he would have felt if he was allocated to the control group:

“Beginning in the group that I am suits me and what my needs are […] as you progress, you do progress to the other group anyway.” [PC2]

“I would have been quite annoyed” [being allocated to the control group] [PI2]

This may be because patients did not know what was involved in the intervention group or that the participant allocated to this group attributed his progression during rehabilitation to the standing intervention. It may be necessary for a future definitive trial to provide more explanation to patients about the trial, specifically that one intervention is not necessarily superior than the other.

Relatives who acted as consultee or were involved in the decision for their relative enrolling in the trial had no preference for group allocation:

> *"No, not really. Either one would have been an advantage to her." [R1]*
>
> *"No anything would be good" [R3]*
>
> *"No, no I didn't even think about it to be honest" [R2]*

Documentation

Most patients and relatives were accepting of the PIS they had been given. However, they were only given one, therefore, had nothing to compare it to:

> *"It's clear and easy to read […] pictures were good" [PC6]*
>
> *"A good amount of information in terms of knowing what you were agreeing to" [PC1]*
>
> *"Initially I thought there was quite a lot of it, but there wasn't really once you started reading it, it was fine. Self-explanatory." [R3]*

One patient suggested some improvements to the PIS:

> *"I think the diagram could have been better. I could see within the diagram the strong points within the standing frame itself and compared to a walking frame [A4 doubled sided PIS], make the picture more specific to the description. Have the scales [foot sensors] on the diagram." [PI2]*

There were mixed views among patients and relatives about whether they preferred written or verbal information about the trial:

> *"[…] it depends what you like and whether you could understand anything" [PC6]*
>
> *"Not all stroke patients can take in the information, also most people who have a stroke probably forget everything after a few days" [PI2]*
>
> *"Not really no, talk to me [would you prefer to have someone talk to you about it or have something the read?]" [PI3]*
>
> *"There's no point [keeping a copy of the PIS], I wouldn't read it again. [PC3]*

In summary, there were mixed opinions regarding trial procedures among physiotherapists; eligibility criteria and the "ideal patient" being the most widely

debated topics. It was apparent that the physiotherapists were accepting of the trial design, however, there was no agreement about the duration of the trial; most preferred a shorter duration/less sessions per week, although only a few physiotherapists acknowledged the impact this would have on intensity of practice. Physiotherapists emphasised that the functional standing frame intervention is not suitable for every patient and recognised how their beliefs about the ideal patient affected recruitment and delivery of the intervention. It was evident that physiotherapists' beliefs and opinions about how the standing frame looked, and its transferability to the ward and home environment, potentially influenced implementation of the intervention. Conversely, patients and relatives were largely positive about both the look of the standing frame and the overall trial. Participants and relative expressed how the trial gave them hope about recovery, and their strong will and determination positively impacted on the very high retention during the intervention period.

This theme identified positive and negative experiences of trial procedures, and patients and physiotherapists offered suggestions to overcome some of the barriers or challenges identified. The final theme provides insight into the experiences of using and implementing the functional standing frame programme from the perspective of patients, relatives and physiotherapists.

Theme 4) Experience of using and implementing the functional standing frame intervention

Research capturing participants' perspectives and experiences of being involved in randomised controlled trials is increasingly being undertaken to help inform and improve the conduct of future trials[360]. Understanding patients', relatives' and physiotherapists' experiences of the functional standing frame will

provide insight into which aspects of the intervention may need to be adapted, fixed or flexible.

Physiotherapists' perspectives

Patient's abilities to undertake the intervention

The thoughts and feelings expressed by patients and physiotherapists differed in relation to patients' ability to tolerate the functional standing frame programme. Several physiotherapists considered that patients "can't tolerate" the intervention due to the severity of their stroke and that they were tired, bored, scared, and did not enjoy it:

> *"Even if you're using a standing frame if they're really struggling with their head and trunk they might still need lots of hands on, to be able to get them up, I think patients can find that quite unnerving. I think my experience has been they feel a little bit more secure using the tilt table." [Physio 7 FG]*
>
> *"I think as much as we tried to be creative, people often got bored […] and they weren't necessarily enjoying it because they felt so scared, because they knew they didn't have their midline" [Physio 5 FG]*
>
> *"They weren't tolerating it, they were getting really fatigued" [Physio 8 FG]*

Some physiotherapists stated that the intervention was "cruel" or "too extreme" for patients with very severe stroke. Physiotherapists highlighted how this affected the duration of sessions and the number and frequency of rests breaks they provided for patients. *"[…]it felt really cruel, they were trying to lift their head up and they were tolerating five minutes and it was just pointless for them and it would have … yeah, that presentation it's just felt wrong with […] and it just felt like it was too extreme […] it felt cruel. [Physio 8 FG]*

Acceptability of the functional standing frame programme intervention

One physiotherapist said the intervention was "cruel" or "too extreme" [Physio 8 FG] for patients with severe stroke. Additionally, another physiotherapist said "you need quite a lot of hands; sometimes three or four people so it's obviously

just taking other therapists off the ward but that's the only negative thing about it" [Physio 4]. These comments suggest that the intervention may not have been acceptable to some physiotherapists.

Patient's perspectives

Adverse events

Some patients recalled adverse events they had experienced during the functional standing frame intervention, and felt the intervention "woke up" an old injury or exacerbated pre-existing problems:

> *"It exacerbated problems I already had which was restless legs. I found that the more I did on the standing frame the more my restless leg became active at night […] That's when I hurt my groin. I put a lot of pressure on my hip doing that, that's when I felt my groin pull." [PI2]*
>
> *"Well I've got a back injury from years ago and that kicks in you know, bottom of my back. I strained it 30 years ago. It comes back every now and again." [PI3]*

Despite adverse events, this did not affect participants continuing with the functional standing frame programme, nor impact negatively on their experience of the intervention.

Patients' abilities to undertake the intervention

Patient participants reported that whilst they needed and appreciated rests, they were reliant on their physiotherapist to encourage and motivate them, voicing a resistance to a protective or paternalistic approach that some physiotherapists may have adopted:

> *"You've just got to give it a go. I mean the girls say to me do you want to sit down, and I say yes please. I don't have a problem if I sit down, then I'm okay again then." [PI3]*

“The physio said to me the other day, do you want to stop now if you’re too tired, if you want to stop we can stop, I went “no”, […] let’s carry on you know.” [PI2]

“I'm in a position that I need to be pushed” [PC3]

Patients reported valuing the encouragement and support from their physiotherapist:

“I accept their professional opinion […] I trust them. I have confidence in professionals […] encouragement of the girls keeps me going.” [PI3]

Some patients acknowledged that whilst they did not necessarily want to be doing physiotherapy, they recognised that it was an integral part of their recovery:

“I don’t fancy doing all this physio to be quite honest, but I’ve got to get better and I’ve got to try to do it […] If you want to get better you’ve got to put some go yourself into it.” [PC6]

“I’m in a position that I need to be pushed. Realising that it’s for my own good that we’re doing things, but it’s still things that were painful and hard, and quite within their right for my benefit. Sometimes I find it hard to put it into words and I go around the houses.” [PC3]

“I didn't want to do it but when I bloody done it I felt great, I did honestly. It made me feel great.” [PC4]

Patients appeared aware that they have severe and profound physical and non-physical impairments post-stroke, and that undertaking physiotherapy is challenging and not something they want to be doing. However, they acknowledged that physiotherapy is an integral part of their rehabilitation and they need to be encouraged and pushed by their physiotherapists to achieve their hopes and goals of recovery. Patients emphasised the trust and confidence they had in their physiotherapists, and, it is therefore likely that if physiotherapists do not accept or support the intervention, this has the potential to affect how much encouragement and support they offer patients, which may affect adherence with the intervention.

Acceptability of the functional standing frame programme intervention

Patient participants were mostly positive in their comments about the intervention, especially in terms of the opportunity it provided them to get up, get out of bed and stand up regularly after their stroke:

> *"That would be good, laying down in a bed like this and doing nothing except talk to people is not getting anywhere" [PI1]*
>
> *"You can't like it all but it's for the great good, so just go with it" [PI3]*
>
> *"Gets you where you want to be [standing up]" [PI2]*
>
> *"I think it's useful because it gives you a feeling that you're not useless that you may be able to get some of it back again" [PC5]*

There were no negative comments, but some participants expressed indifferent thoughts or feelings about the intervention:

> *"it was alright" [PC1]*
>
> *"I suppose I'm half inclined to agree, but at the same time I'm not entirely convinced" [Is it a good idea to practise standing up after your stroke?] [PI4]*

Relatives were positive about the idea of the functional standing frame programme, identifying both physical and non-physical potential benefits:

> *"The benefits of going through the standing frame are paying dividends […] But also, I think it gives you a bit of sense of purpose and a sense of achievement […] I think it's good. I would imagine you'd lose a lot of confidence if you're lying down a lot" [R2]*
>
> *"Definitely yes, it's a good idea" [R3]*

This theme highlights the impact that the therapeutic relationship had on implementing the functional standing frame programme. Some physiotherapists adopted a paternalistic approach, believing that patients were unable to tolerate the intervention; this affected recruitment and intervention adherence. The data suggested that physiotherapists sometimes deviated or violated the protocol by not screening and approaching potentially eligible participants. Further potential

for protocol non-adherence may also exist that may not overtly be identified as a protocol deviation or violation. For example, physiotherapists may not progress or encourage patient participants as much as they would if they were implementing an intervention that aligned with their beliefs, values or pre-conceived ideas about the ideal patient for this intervention. These factors all have the potential to impact negatively on the results of a subsequent effectiveness trial. However, comments from some patients were in direct contrast to the beliefs of these physiotherapists; despite saying they felt exhausted, and that the intervention was arduous and challenging, they expressed a desire to be encouraged and pushed to work hard by their physiotherapist. This information will be invaluable for training physiotherapists when a subsequent definitive trial is undertaken.

5.7 Summary

The results of the qualitative component of this trial have identified a range of barriers and facilitators that may be critical to the success of a future definitive trial. They encompass factors related to: a) the organisation and culture, including teamwork and dealing with changes in working practices as a result of implementing the functional standing frame intervention; b) knowledge, experience and behaviour of both clinical and research physiotherapists; c) patient hopes and expectations and therapeutic relationships with their physiotherapists; d) trial procedures, particularly eligibility criteria and how stroke severity may impact on the ability of physiotherapists to deliver the intervention. The next chapter will discuss these results in more depth to determine the feasibility of a future definitive trial.

Chapter 6 Feasibility trial discussion

A randomised feasibility trial of a functional standing frame programme was conducted, with the primary aim of determining the feasibility of conducting a large scale RCT of such an intervention for people with severe sub-acute stroke.

6.1 Key findings relating to feasibility

This feasibility trial has identified important factors related to recruitment, fidelity, outcome measures, and trial processes. A range of barriers and facilitators have been highlighted that may be critical for the success of implementing a future definitive multi-centre RCT. Beliefs, attitudes and behaviours of physiotherapists influenced many of these factors and will be discussed in this chapter.

6.2 Adherence

Adherence is a key variable influencing the outcome of clinical trials[361]. Various definitions of adherence and compliance exist with lack of agreement, resulting in these terms being used interchangeably. The World Health Organization (WHO)[362] defines adherence as "the extent to which a person's behaviour […] corresponds with agreed upon recommendations from a healthcare provider". This definition is specific to behaviour of the patient, suggesting the responsibility of adherence lies with the patient. But what impact do the beliefs, attitudes and behaviour of the healthcare professionals have on participants' adherence in clinical trials? How do healthcare professionals' beliefs, attitudes and behaviours affect their adherence to trial procedures?

Physiotherapist-related factors

Beliefs and attitudes about stroke rehabilitation held by physiotherapists are likely to affect behaviour and play a key role in the treatments they implement with their patients[363]. Beliefs have been described as 'a cognitive process resulting in a concrete cognition of how we think things are'[364]. Attitudes are considered 'a more complex cognitive state involving beliefs and feelings as well as values and predispositions to act in a certain way'[365]. According to the theory of planned behaviour, behaviour is determined by the attitudes and beliefs that a person has about the likely consequences of the behaviour[365]. This theory may help understand physiotherapists' clinical decision-making in relation to implementation and evaluation of the functional standing frame intervention, as well as their approach to recruiting potential participants into the trial. Some physiotherapists reported that they felt the intervention was either too challenging for people with very severe stroke, or not challenging enough for people with moderately severe stroke, which may result in a negative attitude to recruitment and delivering the intervention to these patients. The converse was also a possibility. Thus, physiotherapists' beliefs and attitudes in this feasibility trial may have affected their behaviour.

The theory of planned behaviour assumes that human beings are rational and make systematic decisions based on available information and experience[361], and that these decisions are planned. It does not, however, take into consideration unconscious bias. Unconscious (implicit) biases are unconsciously and unintentionally held preferences and stereotypes of which we are not aware[366]. The presence of unconscious bias among healthcare professionals has been identified as a concern because it affects clinical decision-making and treatment selection[366,367]. Some physiotherapists in the

interviews and focus group in this feasibility trial reported preferences for specific treatments, dependent on patients' stroke severity.

Physiotherapists' and Occupational Therapists' beliefs were cited as a barrier to implementing evidence-based stroke rehabilitation recommended in national clinical guidelines[368]. They had their own beliefs about treatments that were not supported by current evidence and this affected their behaviour. Therefore, for the success of a future main trial it is important to consider how this behaviour may affect physiotherapists delivering a protocolised intervention. For instance, one study demonstrated that when considering implementing body weight support treadmill training, physiotherapists weighed up the time taken to set up patients with a harness and two physiotherapists against the potential outcomes of using a much simpler treatment which impacted on their behaviour[368]. Physiotherapists in the SPIRES trial appeared to have similar thoughts, weighing up the implementation of SPIRES against their usual practice. For example, in the focus group and interviews some emphasised the physical effort and staff resources required to facilitate participants with very severe stroke in the early stages of the programme. Some physiotherapists in the focus group suggested a potential solution for a future main trial would be for participants who lack head and trunk control to commence the trial in a tilt table, and progress to the standing frame once head control and aligned static sitting balance for a specific number of seconds has been achieved. The tilt table allows people with severe disability to stand up, weight bear and practice movements to improve head and trunk control whilst being fully supported[369,180]. Identifying solutions such as this may increase the willingness of physiotherapists to adhere to the protocol and trial procedures in a future main trial.

It is important to consider if the participants' medical history influenced physiotherapists' adherence to the protocol with regard to implementing the intervention, either consciously or subliminally, as this may warrant review of the eligibility criteria. Most participants in the intervention group had two or three co-morbidities, most commonly osteoarthritis, joint replacement and coronary heart disease/hyper- or hypotension. There did not appear to be any relationship between co-morbidities and adherence in standing duration or sit to stand repetitions, thus data did not suggest participants' medical history affected physiotherapists' or participants' adherence.

Physiotherapists reported that patients were bored and did not enjoy sessions. It is notable, however, that 91.0% of sessions were recorded as being "enjoyed" by participants, and the interviews highlighted that the participants did not report being bored or scared. It is possible that physiotherapists themselves become bored over the duration of the recruitment period or had an erroneous perception of patient boredom; it would be of interest to explore this in future research. Physiotherapists' attitudes and behaviour appeared to change during the trial time course, as evidenced by data from the interviews and focus group which were conducted at various time points from three months onwards from recruitment commencing. Initially the interviews highlighted how physiotherapists spoke positively about the trial and the intervention, but these attitudes appeared to change over the course of the trial. Some of the reasons for this will be discussed later in this chapter, in relation to organisational culture.

Awareness, understanding and translation of evidence-based interventions for stroke rehabilitation varies among physiotherapists[370,371] and healthcare organisations. Some therapists rely on tacit knowledge and clinical experience

instead of research findings when making decisions about which physiotherapy treatments to deliver whilst others utilise the evidence base to inform their clinical reasoning[372,373]. This variation was evident in the comments made within the interviews and focus groups of the therapists engaged in the trial. One physiotherapist, for example, said that delivering the intervention "felt really cruel" and "it was just pointless" and deemed that the participant was only able tolerate five minutes standing. In contrast, another higher banded physiotherapist with more clinical experience and a post-graduate neurological practice qualification clearly identified the need for intensity of practice, commenting that "physiotherapists with less clinical experience in stroke are not adept at pushing and progressing patients on as much as more experienced physiotherapists". These comments support the notion that the way in which physiotherapists gain their knowledge may impact on their values and beliefs about treatment selection, which, may in turn, influence their conduct in implementing a trial intervention, even when it has been protocolised.

Within the context of the SPIRES feasibility trial, it is important to establish physiotherapists' adherence to the trial protocol and delivering the intervention as specified in the protocol. This is known as treatment fidelity[374]. Attaining and demonstrating treatment fidelity is critical in the development and testing of evidence-based interventions. Fidelity was assessed at three sites. This identified that the intervention was not delivered at one site as specified in the protocol, as illustrated by the account of one participant with dementia who completed only seven out of 21 sessions. The most common reasons documented for non-completion of sessions was: "the participant was not a priority" or there was "insufficient staffing". This could have been reflected at other sites but was not identified in the sessions observed for fidelity checking.

Rehabilitation potential is judged by clinicians at an individual patient level to determine when rehabilitation begins, the intensity of rehabilitation that is required and can be tolerated to be effective, and when further rehabilitation intervention would fail to deliver meaningful outcomes for patients[375]. People with severe stroke have been reported to make a slower and less complete functional recovery during inpatient rehabilitation when compared to those with mild or moderate stroke[376]. Physiotherapists have been shown to focus their resources on “high priority” patients who they perceive more likely to have greater rehabilitation potential[372]; providing them with more regular, and longer physiotherapy sessions than those perceived as not making much physical progress[373,374]. It may be that physiotherapists in SPIRES deemed some participants to lack rehabilitation potential, which may have affected their adherence to implementing the protocol. However, this was not overtly expressed. A deeper exploration of this may have provided useful insights into whether this was the case, and if so, how this might be dealt with in a future definitive trial.

Clinical Guidelines[3] recommend daily mobilisations which encompass sitting out of bed, standing or walking delivered by appropriately trained staff using appropriate equipment. However, there is no specific guidance as to how to implement this with varying severities of stroke, and there is a vast difference in ability and disability for people with mild, moderate or severe stroke. National clinical[3] guidelines do not explicitly recommend the use of standing frames, but state: “Patients with difficulty moving early after stroke who are medically stable should be offered frequent, short daily mobilisations (sitting out of bed, standing or walking) by appropriately trained staff with access to appropriate equipment, typically beginning between 24 and 48 hours of stroke onset. Mobilisation within

24 hours of onset should only be for patients who require little or no assistance to mobilise". There is no definition for "frequent" or "short" and this is left open to interpretation, but people with stroke are recommended to accumulate "at least 45 minutes of each appropriate therapy every day, at a frequency that enables them to meet their rehabilitation goals". The 'active ingredients' of neurorehabilitation which includes stroke is unknown[237], therefore, the lack of specificity in the guidelines are unsurprising. Therefore, this is likely to result in physiotherapists selecting treatments based on their preferences and/or experience as opposed to evidence.

Opinions varied about the level of ability required by patients to use the standing frame, which is unsurprising given the lack of evidence-based guidance about their use. This is likely to have contributed to the variation in their use within this trial. Furthermore, there is no consensus on the optimal rehabilitation interventions for people with severe stroke[377]. The AVERT[378] trial concluded that mobilising within the first 24 hours post-stroke was harmful. It is possible that the physiotherapists engaged in SPIRES may have been cautious in implementing the standing programme intervention in light of any potential negative consequences; as alluded to by some physiotherapists in the interviews when they commented that they felt the SPIRES intervention was "too early". It is noted however that SPIRES participants were beyond the 24-hour timeframe from stroke onset (time to consent was 3-32 days). One further explanation for the lack of adherence to the protocol might therefore be that the physiotherapists' interpretation of the AVERT results[378] had influenced their decision making.

This explanation also suggests that the physiotherapists may have been protective or paternalistic towards their patients. Paternalism in clinical trials

implies that clinicians are deciding which patient they believe is most suitable for a trial, and patients are being prevented from making decisions for themselves[379].This suggestion of paternalism was reflected by some of the comments made by physiotherapists in the interviews and focus group in relation both to recruitment and protocol adherence. It has been shown that paternalism within clinical trials erodes patient autonomy and can introduce selection bias and reduce the generalisability of a trial's results[379]. However, approaching patients and relatives within a few days of a life changing severe stroke to discuss research is acknowledged as being a daunting prospect, and it is understandable that some clinicians may have felt uneasy. Of interest, the SPIRES participants appeared to resist a paternalistic or protective approach by declining rest breaks and/or continuing the session when the physiotherapist suggested they stop. Additionally, all participants and relatives interviewed agreed that all patients should be offered the opportunity to enrol in SPIRES, despite the devastating and life-changing event and severity of their stroke and impairments.

Physiotherapists' attitudes and beliefs have been highlighted as a common barrier in the implementation of stroke clinical guidelines, evidence-based interventions, and clinical and rehabilitation trials[368,370,250]. This also appeared to be the case in this feasibility study. How to address these issues in the long-term for the benefit of future trials including SPIRES will be discussed in Section 5.13 Future directions.

Patient-related factors

Patient-related factors will be discussed using the COM-B model[380]. COM-B is a simple model to understand behaviour and has three layers at its core: Capability (psychological or physical ability to enact the behaviour e.g.

comprehension and reasoning); Opportunity (the physical and social environment that enables the behaviour); and Motivation (reflective and automatic mechanisms that activate or inhibit behaviour). COM-B forms the hub of the behaviour change wheel[380].

Capability

So far, this chapter has explored the beliefs, attitudes and behaviour of physiotherapists and their potential impact on adherence to the SPIRES trial intervention and recruitment. But it is also important to explore patient-related factors when discussing adherence and fidelity of the intervention because these two factors are related. Fidelity of the intervention was assessed in several ways; whether participants attended treatment sessions, reasons why they did not attend or complete sessions, and the activities they completed during these sessions. As previously described, all SPIRES participants had a severe stroke, typically with multiple physical, sensory and sometimes cognitive and communication impairments. It would not be unreasonable to surmise that the relatively low adherence (only 45.4% of sessions were completed) was because of the severity of these impairments. However, the case reports recorded that almost a third (27.9%) of sessions were not completed due to insufficient staffing, with 10.3% due to participants being unwell, and 11.5% due to participant withdrawal. Thus, participant impairments did not appear to be the primary reason for non-attendance of sessions.

Experiencing a stroke can suddenly create a state of dependency, where participants may lack control over their daily lives[381]; with reliance on health professionals to guide their rehabilitation. However, patients may want to take an active role in their rehabilitation[382]. If participants are passive during their rehabilitation, sessions will be determined by physiotherapists' knowledge,

experience, beliefs and attitudes which may have affected participant's adherence, as discussed in physiotherapist-related factors above. Conversely, participants who take an active role in their rehabilitation may request to work through the tiredness, request to sustain or increase the intensity which may impact on the intensity of the session.

Opportunity

Patients needed to be made aware of the research project in order to take up the opportunity of engaging in it. However, in SPIRES, as is the case with most clinical trials, health professionals to a certain extent acted as "gatekeepers"[383] to their involvement, by the level to which they raised awareness of the trial with them. This aligns with the previous discussion of paternalism, in physiotherapist related factors.

Motivation

Some participants reported they were exhausted during their sessions and were reliant on their physiotherapist to encourage and motivate them to continue their sessions. Conversely, some participants reported an internal motivation to "push through the tiredness", declining to end a session when their physiotherapist suggested they stop. This aligns with existing literature reporting that patients do not mind being pushed to work hard during rehabilitation, recognising this can be helpful when their motivation is lagging[381]. Correspondingly, it has also been demonstrated that a lack of perceived encouragement and support from professionals may demotivate patients during their stroke rehabilitation[382] which can negatively affect rehabilitation outcomes.

Motivation is multifactorial but there is no consensus for its concept[385]. However, motivation in rehabilitation is considered important due to its impact on patient outcomes[384,386]. Motivation levels in people after stroke have been

distinguished as high and low[385] and internal and external[386]. Highly motivated patients are aware of the importance of their active participation in rehabilitation and the significant improvements that may occur in their condition. In contrast, people with low motivation for rehabilitation show lower commitment to achieving fast recovery[384]. Motivation and adherence are related[385]; both appeared to fluctuate for SPIRES participants, as reflected by their comments in relation to acceptance of the stroke, change in function and role, apprehension about the future and impending discharge from hospital. Previous authors have highlighted that patients consider their motivation toward physical rehabilitation as being a fluid condition that can be affected positively or negatively by their treating team[381]. It is possible that in the SPIRES trial, some physiotherapists may have affected participants' adherence and motivation (intentionally or unintentionally) due to their beliefs and attitudes about the intervention, as indicated by the language used by therapists in the interviews and focus group when they referred to the standing programme as being, for example, "ideal" or "not suitable".

It was anticipated that fatigue and OH may impact on completion of SPIRES intervention sessions, hence the minimisation process accounted for these two factors, which proved to be appropriate since most participants with fatigue and OH spent less time in standing (Section 4.8.4, Chapter 4). Prevalence of OH was lower than expected in this sample. Orthostatic hypotension was slightly higher in the intervention sessions (n=6) compared to the minimisation assessments (n=4) (reflecting differences in how this was measured) but did not reflect the high prevalence (52%[109]) identified in the systematic review (Chapter 2). It is possible that the lower prevalence of OH may be attributed to the sit to stand repetitions undertaken; the systematic review identified that physical

manoeuvres such as leg muscle pumping/contractions and bending forward minimised OH[387]. The low prevalence of OH during the physiotherapy sessions may also be attributed, at least in part, to low adherence to the sessions, because over half of the 945 sessions were not completed. Although prevalence of OH in SPIRES was not as high as anticipated, it is important to assess and monitor it, due to the risk of increased disability and mortality as a result of cerebral hypoperfusion as discussed in Chapter 2. In a definitive main trial, it is recommended that OH is recorded as an adverse event.

Prevalence of fatigue in this sample was high. Although it was not the primary reason for non-completion of intervention sessions, several physiotherapists commented that they felt some participants were unable to tolerate the intervention, and as a consequence chose to either shorten the duration of the patients standing session or to cancel it. Given the impact that fatigue appeared to have on adherence to the protocolised intervention, it could be argued that a systematic review of interventions to treat fatigue is warranted prior to a definitive main trial to determine whether these might be utilized in order to enhance standing session times/frequency.

Organisational and cultural factors

The results of SPIRES feasibility trial were broadly aligned with the findings of a qualitative process evaluation undertaken in the AVERT trial, a large multi-centre international stroke rehabilitation trial delivering a complex intervention of early mobilisation in people with acute stroke[249]. They identified organisational or workplace barriers that are mirrored in the results of SPIRES: the fast paced, discharge driven culture of acute/sub-acute stroke units, where rehabilitation had low priority and there were competing organisational priorities which included a resistance or lack of support/encouragement from the therapy team

and wider rehabilitation team management, repeated organisational changes, and an absence of a research culture. Insufficient time and inadequate staffing levels were also identified by Luker et al., (2016). However, neither the participants of this process evaluation (the health professionals) nor the authors identified any solutions or facilitators to any of these organisational barriers.

Some organisational barriers such as lack of time and inadequate staffing are not exclusive to clinical trials and appear to be reflective of daily clinical practice in stroke rehabilitation. They have been commonly reported as barriers to implementing evidence-based stroke rehabilitation[388]. Therefore, it is unsurprising that the additional workload of a clinical trial may exacerbate pre-existing organisational challenges and barriers. The organisational barriers identified in SPIRES are worthy of acknowledgement in terms of their impact on recruitment and intervention implementation. Such barriers may be modifiable or non-modifiable, both of which need to be factored into the planning of a future main trial and potential solutions identified.

Opinion varied among physiotherapists as to how stroke severity affected their ability to deliver the intervention in relation to resources. It is widely known that rehabilitation of people with severe stroke is associated with increased resources compared to people with mild or moderate stroke[389]. Thus, it was unsurprising that physiotherapists identified that delivering the intervention with this sample of people with severe stroke challenged existing resources, which at many sites were already reduced. Reduced staffing levels are identified in the literature as a reason why people with stroke do not receive the recommended amount of active therapy during inpatient stroke rehabilitation[3]. Staffing levels for physiotherapists at all four sites were lower than recommended in National Clinical Guideline for Stroke[349] periodically throughout the trial due to vacancies,

annual and maternity leave and sickness etc. This combined with the natural ebb and flow of integrating new, (sometimes less experienced) staff members, exacerbated difficulties with trial procedures such as the consistent implementation of the intervention and recruitment of participants.

The number of beds in a stroke unit determines the number of staff; bed numbers in the four sites ranged from nine to 21. Staffing levels were significantly reduced at one site (a nine bedded unit, staffed by two physiotherapists) for several weeks which resulted in recruitment stopping at this site. This highlights the need to consider the size of the stroke unit prior to involving a unit in a definitive main trial.

The perceived burden of a trial by the staff members within a unit may also influence consideration of engaging the unit in a future trial. For example, the interviews and focus group highlighted that some physiotherapists remarked that the number of physiotherapists required to implement the intervention with people with very severe stroke, was too great, especially when it had a negative impact on staffing and equity of care between trial and non-trial patients; creating moral dilemmas for some of the physiotherapists. For a main trial, there may need to be a more flexible approach to recruitment; with a pro rata approach to participant recruitment numbers dependent on staffing levels. Additionally, changes in the approach to the intervention protocol, such as allowing some participants to start standing in the tilt table before progressing to the standing frame (Section 5.4) might also help to better manage the challenges faced in terms of staffing levels.

Studies have shown that reduced staffing can determine what interventions patients receive[372]; limiting therapy options, reducing patients' opportunities for standing or walking.

In SPIRES the most commonly adopted positions for participants during control group sessions were lying and sitting, which could be delivered by one physiotherapist, freeing up resources to treat other patients/participants. Preference for treating patients in sitting and lying may also be related to physiotherapists' knowledge and understanding of evidence-based stroke rehabilitation, which can, in turn, influence the shared beliefs and attitudes of physiotherapists and organisational culture.

Organisational culture is defined as a set of beliefs, values, and assumptions that are shared by members of an organisation[390]. Healthcare organisational culture has been described as a metaphor for some of the softer, less visible, aspects of health service organisations[391] which may influence treatment selection or adherence to clinical trial protocols. Healthcare organisational culture is complex and has been categorised as three layers (1) visible manifestations which include a range of behaviours seen as embedded, normal and acceptable clinical practice; (2) shared ways of thinking including shared values and beliefs, and (3) deeper shared assumptions that are largely unspoken often unconscious expectations, beliefs and values that underpin clinical practice[392]. Together these layers reflect a shared and commonly understood view of the clinical workplace. It was observed that the culture within each of the four SRUs in SPIRES appeared to vary, in relation to shared values and beliefs about the intervention, and that this affected recruitment of participants into the trial and adherence to the trial protocol.

A research culture has been associated with benefits for patients, clinicians, and the healthcare organisation through improved treatment interventions, enriched career opportunities, and enhanced reputation[393,394]. However, there appears to be a lack of consensus on what defines a successful research

culture. Comments in the interviews and focus group drew attention to the notion that a weak research culture was evident within in some of the units engaged in the SPIRES trial. For example, some physiotherapists reported that an evidence-based treatment approach was “not highly thought of within their organisation”. This may affect how supportive therapists and the wider multi-disciplinary team were about being involved in implementing the SPIRES trial. Research experience (determined by GCP, curriculum vitae and site visits) varied among sites and physiotherapists and this is likely to have influenced the implementation of trial processes.

Adherence summary

Patient, physiotherapist, organisational and cultural factors all affected the implementation of trial processes in this feasibility trial. None of the participants in the intervention group achieved complete adherence to any aspect of the standing programme (30 minutes of standing and 8-12 sit to stand repetitions or graded increase of 30% each week for a minimum of five sessions per week for three weeks).

Physiotherapist and patient-related factors affected adherence however, the interviews did not specifically explore adherence in depth. A future study, undertaking ethnographic research focusing on this question may be warranted to explore in more depth.

6.3 Safety

Safety risks were considered an important aspect of feasibility, but the risks associated with taking part in this trial were assessed as low[351] None of the AEs and SAEs were deemed related to the trial and most were reported during the follow-up period. Safety was never highlighted as an issue by physiotherapists,

participants or relatives at any time during the trial, and did not appear to have a profound effect on adherence to the standing programme.

Just over a quarter of participants died (26.7%, n=12) which was higher than the 7.6% deaths reported in AVERT[378]. This indicates that the appropriate participants were recruited because people with severe stroke have an increased mortality risk[365]. It is important to consider age. Age is the strongest predictor of adverse stroke outcomes[396] and 60% of SPIRES participants were ≥80 years (mean age 80.3 years), compared to 26% ≥80 years (mean age 72.5 years) in the AVERT trial. Nearly 40% of patients admitted to UK stroke units are ≥80 years of age[397], therefore, it is important where possible not to exclude people ≥80 years in stroke research. Additionally, people with stroke, their relatives and physiotherapists felt there should not be any age restriction for entry into the trial. However, increasing age was associated with higher mortality rates in SPIRES, which aligns with other research[398], therefore, a definitive main trial could stratify for age.

Mortality rates in a six-month trial of prolonged standing for people with severe stroke appeared to be similar to SPIRES[97]. When comparing the 12-month mortality for people with stroke, mortality in SPIRES (26.7%) was much lower than the 41% and 40.3%[309,310] observed in (not rehabilitation) studies investigating the long-term survival rates post-stroke. Infection (respiratory) and further stroke were the two reasons disclosed for cause of death for five SPIRES participants, cause of death was unknown for seven participants. Active infections at recruitment were an exclusion factor (medically unstable) but given the long term follow up it is not possible to mitigate for these causes of death.

Frailty is a syndrome of decreased reserve and resistance to stressors resulting from a cumulative decline across many physiological systems leading to vulnerability and adverse outcome[399]. Several measures of frailty are used in clinical practice[400], but pre-stroke frailty was not measured or captured in SPIRES. A stroke may be considered as a significant stressor, and low physical function components of frailty, measured by walking speed and grip strength, are the most consistent determinant of shorter survival and lack of post-stroke recovery in cognition and activities of daily living[396]. A definitive main trial should consider including pre-stroke and post-stroke frailty measures which could help identify individuals at the greatest risk for poor stroke outcomes.

6.4 Design

SPIRES was a multi-centre feasibility RCT, and the justification for this is discussed in Chapter 3 (Section 3.5). If SPIRES were to proceed to a definitive main trial an alternative design could be a cluster RCT which would randomise stroke rehabilitation units as opposed to individual participants, thus avoiding treatment group contamination and the possibility of enhancing adherence[401]. However, on questioning, the physiotherapists' preference was for the current trial design. They acknowledged a cluster RCT may be preferable in terms of blinding but felt delivering both control and intervention groups at each site would help maintain motivation and interest for themselves, challenge their practice and be easier to manage the workload associated with the standing intervention. Further, implementing a flexible recruitment rate that mirrors staffing levels, as stated previously, would help to address workload issues.

An alternative approach is a cluster stepped-wedge RCT. This would address the desire to deliver control and intervention groups at each site because

clusters initially serve as a controls before receiving the intervention at a subsequent time step; eventually, all clusters receive the intervention[402].

Although a feasibility trial does not enable conclusions to be drawn about effectiveness of an intervention[238], in SPIRES the greatest improvements in function, as evaluated by the outcome measures, occurred in the first three weeks with smaller changes continuing up to six months. This links to the evolution of physiological changes in stroke (discussed in Chapter 1 Section 1.3) wherein the most rapid changes in impairment and function occur in the first three months but continue at six months and beyond[11]. Therefore, a factorial design could provide the opportunity to determine the clinical and cost-effectiveness of the SPIRES intervention at two time-points: inpatient sub-acute stroke rehabilitation (early) and the community (late) (see Figure 6.1).

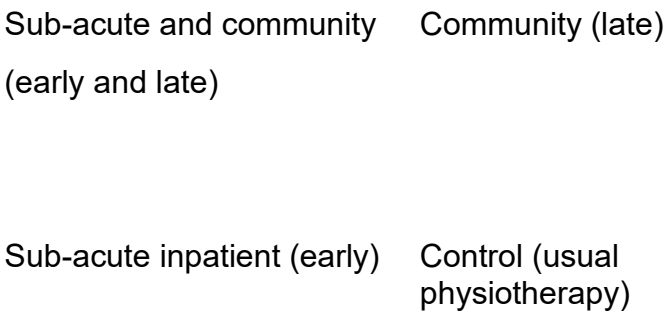


Figure 6.1 Proposed factorial design

A factorial design would allow the effects of two interventions to be investigated independently in the same trial as well as testing if two interventions work in synergy or are antagonist and has been used for evaluating complex interventions in a wide range of health care settings and clinical specialities[403]. However, the trial would need to be appropriately powered to estimate the interaction between the two interventions[402]. Further, the proposed factorial

design is limited by the maximum duration of treatment in the inpatient setting (~18 days-see below) otherwise there would be a confounding factor of differences in treatment duration between groups.

A factorial stepped-wedge cluster RCT has been proposed recently that could be the design a definitive main trial[404]. However, there are several important caveats to the proposed factorial designs for SPIRES: a) the cost implications for delivering the intervention in the community needs to be addressed, e.g. provision of standing frames and treating therapists because therapy provision post-discharge varies geographically, which may be challenging in the current financial environment; b) it is a more complex design that may require more resources to manage; c) a larger sample size will be required; d) consideration of the duration is warranted in relation to the physiological changes the intervention aims to facilitate. Future work will aim to collaborate with a consensus group/expert panel to determine the future trial design.

The duration of the intervention was based on the average length of stay in 2015 when the trial was developed. However, it is important to review whether the national model for stroke care has changed and what impact, if any, this may have on the duration of a future main trial. The most recent data suggests the average length of stay for sub-acute stroke rehabilitation in the UK is 18.1 days (median 6, low IQR 2, high IQR 20.2)[405]. Unfortunately, the Sentinel Stroke National Audit Programme (SSNAP) do not provide a breakdown of data to differentiate length of stay based on stroke severity. This is an average length of stay, and for some stroke units this is 7.3 days. Length of stay varies across the UK, at least in part due to variations in criteria for ESD services (e.g. level of assistance required), and patient case mix. This affects when and where stroke

rehabilitation is delivered, which would impact on the delivery of a future trial which could potentially span both inpatient and community settings.

It is important to consider both pragmatic and aspirational views for the future of stroke rehabilitation. The refrain that delivering high doses in current healthcare settings is not possible has been identified (the pragmatic view)[237]. This aligns with findings from SPIRES that staffing resources and organisational priorities impacted on the delivery of the SPIRES standing programme dose. One might therefore argue that a lower dose be protocolised for the standing programme. A distinct disadvantage of this is that current policy would be the driver for dictating treatment selection and rehabilitation trial design, which may have a detrimental impact on patient outcome[237]. It is argued that a higher dose and intensity may be more costly initially but may result in reduced dependency further along the rehabilitation continuum, a requirement for less formal or informal care, and a higher rate of return to work. All of which may have significant impact on the economic burden of health and social care. The role of clinical research is to challenge current practice in order to reshape and improve rehabilitation services (the aspirational view)[237]; it is maintained that post-stroke rehabilitation must adopt the same aspirational approach[406].

Foot sensors

Foot sensors were provided based on the findings from a systematic review that quantified weight bearing should be monitored in future clinical trials of supported standing[94] and sit to stand practice[407]. This aligns with more recent evidence that asymmetrical weight bearing and weight-shifting ability correlate with gait asymmetries, and rehabilitation strategies that increase the contribution of the paretic limb to standing balance control may increase symmetry of walking post-stroke[408]. However, some physiotherapists remarked

that the foot sensors did not necessarily facilitate a positive outcome and preferred to use their own clinical judgement instead. To my knowledge, the relative reliability and usefulness of physiotherapists' observation versus foot sensors or biofeedback has not yet been empirically confirmed. Of specific relevance to this feasibility trial, despite several iterations in the design and manufacture of the foot sensors, they were deemed by the physiotherapists as unreliable and temperamental which made delivering the intervention more difficult. Some physiotherapists were also not convinced participants liked them, suggesting they may have triggered anxiety.

The foot sensors would therefore need to be developed further with physiotherapists and people with stroke if they were to be used in a definitive main trial.

Who should deliver the intervention?

SPIRES intervention was delivered by physiotherapists, and during the design of the trial the potential for OTs and therapy support workers also delivering the intervention was discussed. The consensus was that it should be led by physiotherapists due to their knowledge and experience in analysis and facilitation of movement. However, prior to progressing to a main trial, this needs to be discussed on a wider scale because working practices and beliefs varied throughout the sites, and OTs and therapy support workers used the standing frame in their treatment sessions. This approach may help to address the challenges posed by staff shortages and share the workload with other members of the multi-disciplinary team.

Fidelity checking

Fidelity checking in SPIRES formed part of the process evaluation, and given the significant issues identified with low adherence, monitoring fidelity in a

definitive main trial is warranted. Caution in the interpretation of the fidelity data is important since the number of fidelity checks undertaken in this feasibility trial was low (one control and one intervention session once at each site) and may not provide a true reflection of the overall fidelity status. More frequent monitoring may have had the advantage, not only of increased confidence in the fidelity data, but also in affording the opportunity to address implementation issues during the trial. Implementation fidelity can affect the credibility and utility of research[409], and a conceptual framework may facilitate a way of measuring and monitoring fidelity in a future main trial. The Implementation Fidelity Framework (IFF)[409] incorporates components of implementation fidelity and factors that may influence the degree of fidelity (moderating factors). Measurement of implementation fidelity is a measurement of adherence, which includes content, frequency, duration, and coverage (dose). The framework was empirically tested and modified with two additional moderating factors: context and recruitment[410]. In a future main trial, it is suggested that the fidelity data gathered should be analysed regularly so that any training or logistical issues identified could be addressed in a timely manner.

Assessment timepoints

It was feasible and acceptable to participants to be assessed at five timepoints: baseline, post-intervention period (3-weeks), and 15-, 29- and 55-weeks which represent 3-, 6- and 12-months post-intervention period. Previous trials of prolonged standing have varied in duration, with final time-points of three and 12 months[95-97]. It is important to consider the predicted physiological and behavioural changes to determine assessment timepoints for a definitive main trial for SPIRES. The Stroke Recovery and Rehabilitation Roundtable taskforce[11] have developed a framework that encapsulates definitions of critical

time-points post-stroke that link to the currently known biology of recovery. They report the current understanding of brain repair processes suggests that most of the behavioural recovery, and the rapid changes occur in the first weeks-to-months post stroke for most people, and they recommend assessing from hyper-acute to chronic (>6 months) but do not explicitly recommend a final time-point beyond six months. Assessment at three months is considered essential for all stroke trials that are testing sensorimotor interventions, and at least six months for trials conducting an economic evaluation[411]. Therefore, it is suggested that a definitive main trial should assess at baseline, post-intervention, 3- and 6-months post-intervention (but not 12 months).

In stroke rehabilitation trials, it is also important to consider the impact of other therapies beyond the trial that may affect functional outcomes, given the multi-disciplinary and multi-service nature of input[3]. It is therefore recommended that a resource use questionnaire is used to systematically record the multi-disciplinary input received over the timeframe of the trial.

6.5 Recruitment and retention

Successful clinical trials are dependent on effective recruitment and retention of the target sample size[352]. If this cannot be achieved, there are implications for statistical power and internal and external validity[4121]. Slow recruitment also has practical and financial implications, as it can delay trial completion, which, in turn, may impact on the timely impact of research findings on clinical practice[352].

Challenges with recruitment and retention are widely known for stroke rehabilitation trials and RCTs in different specialities, and several studies have provided valuable insight into the barriers and facilitators[352,412-414].

Recruitment

SPIRES recruitment target was 50 participants over 12 months, and the feasibility indicator for success was ≥70% of 50 participants. Forty-five participants were recruited over 10 months representing 90% of 50 participants (Section 4.5 Chapter 4) demonstrating success for this feasibility indicator. It is also important to determine the willingness of physiotherapists to recruit. This was measured by the percentage of patients screened and approached from the number of eligible admissions. The feasibility indicator for eligibility (≥50% of admissions screened and ≥75% of eligible participants approached) was achieved. SPIRES had a two-stage screening approach: 1) to determine eligibility for stroke severity (mRS 4 or 5) on admission; 2) formal screening once stroke severity confirmed. Whilst the parameters for success were achieved, it is important to consider reasons that other potentially eligible participants were not screened and/or approached.

It was apparent from the interviews and focus group that there were instances where eligible patients were denied the opportunity to make their own decision about participating in SPIRES. Some physiotherapists reported to being selective about which patients they did and did not screen or approach, deeming that some patients were either “too good” or “too impaired” for the intervention.

Some sites were more “on-board” (as reflected by willingness to recruit etc.) than others, and this has been identified in other stroke rehabilitation studies[250]. Willingness to recruit may have been affected by clinical equipoise; the assumption that a superior intervention is not present (for either the control or intervention group) in a RCT, or personal equipoise; the assumption that the clinician involved in the research trial has no preference or is truly uncertain

about the overall benefit or harm offered by the treatment to their patient[415]. On reflection it was perhaps naïve to assume that physiotherapists would all have clinical and personal equipoise and fully adhere to trial procedures. It raises the question as to whether, in addition to the required Good Clinical Practice (GCP) training, further training might be necessary on issues of this nature to optimise the success of a future definitive trial.

Recruitment may also have been affected by clinician gatekeeping which has previously been identified as problematic in health research. It is a complex ongoing process that has a powerful impact on the extent to which a research study is successful[415] and covers several of the issues identified in Adherence (Section 5.2). Cherry picking and gatekeeping have been identified in other stroke rehabilitation trials[249,412]. Gatekeepers have been described as 'individuals who have the power or influence to grant or refuse access to a field or research setting'[383]. Gatekeeping in SPIRES may have arisen due to physiotherapists' beliefs and attitudes towards research, an assumption that patients preferred not to participate, a perception that they needed to protect their patient(s) given the doubts they had regarding the suitability of the intervention for the individual patient[417]. It could also be due to their confidence or lack of research expertise as not all physiotherapists had prior research experience or post-graduate education.

A facilitator to minimising recruitment barriers would be a dedicated person (not one of the treating physiotherapists) to screen and consent potential participants, e.g. Research and Development or Clinical Research Network staff. This would address the selection bias and alleviate physiotherapists having to spend time on the consent process and complete associated paperwork.

Consent

Ability of patients to provide informed consent in stroke trials can be challenging due to communication and cognitive impairments that may deem them to lack capacity to make an informed decision to enrol[352]. Ability to consent was a feasibility indicator, and 63.0% (n=29) of participants provided informed consent.

When a participant was judged as lacking the capacity to provide informed consent, a relative of theirs was approached to act as a consultee. Relatives who provided consultee declaration said they “didn’t mind” being approached or making that decision on behalf of their loved one. Relatives can also be gatekeepers, blocking or allowing access to potential participants when acting as consultee[418]. However, this was not an issue in SPIRES. Additionally, there may be a conflict for relatives in their decision making; on one hand considering that their loved one may benefit physically by participating in the trial, whilst also being concerned that they do not want to overburden them given that they have had a severe stroke. This was apparent in the comments from one relative where he spoke of his initial refusal for his wife’s participation because of the potential for her to become “over stressed” and that it may be “too much for her” subsequently reversing this decision following discussions with their children, at which time they “all agreed it was a good idea” and provided assent.

Retention

The feasibility indicator for retention was successfully achieved with ≥60% of participants completing assessments at all five time-points. This included an estimated 40% drop out rate due to mortality, because mortality rates are high in people with severe stroke[309]. Drop-out rates in studies of prolonged standing

were lower than SPIRES: 11.8%[421] 24.3%[95] and one higher with 52% drop-out[97].

Relatives are also important gatekeepers in trial retention. They may support and encourage their relative to do their best in therapy sessions, continue or withdraw even when not acting as consultee[417]. Due to communication and cognitive impairments many participants in this feasibility trial were reliant on their relatives to arrange appointments for follow-up assessments. Despite many relatives having work and family commitments, all granted access for follow-up appointments and were supportive of trial visits.

It is important to look at who made the decision for withdrawals to determine whether any refinements in trial processes are required in relation to this in a definitive main trial.

6.6 Eligibility

An important aspect of a future main trial is eligibility criteria, and in this feasibility trial it was apparent within the interviews and focus group that this was a contentious topic for some physiotherapists. People with stroke were eligible to enrol in the trial if they were classified as a modified Rankin Scale (mRS) Grade 4 or 5.

Physiotherapists identified that including both mRS Grades 4 and 5 encompassed a wide range of abilities and disabilities. Further, some physiotherapists felt the mRS was open to interpretation and several physiotherapists identified no patient is bedridden (mRS Grade 5) due to early mobilisation practises, and participants who were mRS Grade 4 were “too good” because they were walking, even though they needed assistance. This aligns

with existing literature that the main limitation with the mRS is the potential for substantial inter-rater variability[418]. Various approaches to reduce inter-rater reliability have been produced including structured interview[420], training programmes including digital training using vignettes[421] and a simplified mRS questionnaire algorithm[422]. The Rankin Focused Assessment (RFA) differs from other approaches because it encourages the rater to gather information on patient functional performance from all available sources, including patient self-report, caregiver observations, physical therapist notes, medical records, and the rater's own examination and interaction with the patient[423]. Tested in 50 participants with stroke enrolled in a clinical trial, agreement between raters was 93%, (weighted kappa 0.99 (0.98–1.0), and the unweighted kappa was 0.91 (0.82–1.00)). Given the multiple sources of performance and information, the RFA would be beneficial for participants with cognitive impairment including anosognosia and communication impairment.

Some physiotherapists felt that a different measure should be used to determine eligibility. Suggested changes to the trial design such as additional guidance for the mRS which would be incorporated into future training, may alleviate the need for a different measure. However, their suggestion of the Rivermead Mobility Index as an alternative way to determine eligibility will be discussed in Section 5.10 as a potential secondary outcome measure.

The NIHSS was used because some sites reported to using it as part of their usual practice whilst the mRS score is captured by all sites participating in SSNAP audit. The NIHSS has been criticised for limited representation of cognitive and visual dysfunction and bias towards dominant hemisphere functions[424]. For example, truncal ataxia, reduced visual acuity and memory impairments are neurological deficits that affect mobility and function were not

detected by the NIHSS[418]. The NIHSS is recommended for use in all stroke trials by the Stroke Recovery and Rehabilitation Roundtable[411], but they do not provide any justification for this. The NIHSS takes longer to complete and requires training, therefore, it is proposed that the RFA will be used in the definitive main trial instead of the mRS.

6.7 Dose and intensity of rehabilitation

Improving outcomes post-stroke through higher dose (time in rehabilitation or number of repetitions) and intensity (dose per session)[83] has been consistently highlighted as a critical component of therapy after stroke[425]. However, clinical trials investigating the effectiveness of high-dose and high-intensity have predominantly targeted upper limb rehabilitation[237,426]. These trials have included repetitive practice, which several other clinical trials have investigated for lower limb function but were of moderate quality evidence[98]. Although repetition of functional movement was a major mechanism of action for studies included in this Cochrane review, the number of repetitions was rarely available. Therefore, this review investigated the impact of functional task specificity more than the element of repetition (dose).

Studies investigating high-dose and high-intensity training[237,426,427] have focussed more on time in rehabilitation (hours or minutes per day or a total time over weeks), and less on specific activities and repetitions in each session. Time in rehabilitation does not necessarily equate to intensity, and it is important to consider the activities performed during the session and their impact on functional outcome. SPIRES participants in the control group had longer sessions but undertook activities in supine and sitting that are not as challenging as activities in standing (supported or unsupported). Physiotherapists reported that being involved with SPIRES challenged their

practice, prompting them to reduce the amount of rest times, and increase active movements and time in standing during treatment sessions, suggesting contamination. During a high intensity upper limb programme[237], a wide variety of treatment options were used to supplement two daily sessions each of physiotherapy and occupational therapy.

It is important to discuss the biological and physiological processes that SPIRES intervention aimed to address. Within the three weeks, improvements in strength were not anticipated, because evidence suggests improvements in strength take at least eight weeks to occur[428]. The main aims were to minimise secondary neuromuscular changes (Section 1.5 Chapter 1) and positively influence neuroplasticity (Section 1.3 Chapter 1), specifically experience dependent plasticity through motor relearning based on motor learning theory. Motor learning is the study of the processes involved in acquiring and refining motor skills and the variables that promote or inhibit that acquisition[429]. An in-depth discussion on motor learning is beyond the scope of this thesis, however, some important aspects pertinent to the standardisation of the SPIRES intervention group will be discussed.

Learning is a relatively permanent change in a person's capability to execute a task as a result of practice or experience[430] whilst performance is a temporary expression of skill[430]. Repeated, blocked practice may improve performance within a session, but less learning gains are made. Conversely, variability of practice may result in worse performance within a session but greater learning gains and generalisation to new tasks[498,430]. Generalisation of learning to new tasks is deemed of critical importance in stroke rehabilitation, to help improve performance in different activities of daily living[431]. In SPIRES, variability of practice could easily be implemented for sit to stand by varying seat heights and

seats (with or without arms), feet position and speed, and changing the environment by practising in the gym or by the participant's bedside. However, this was not included in the work instruction or captured in the CRFs, thus could be incorporated into a future main trial and be emphasised in the training.

Some physiotherapists reported to "chop and change" and vary what they did during treatment sessions. Unfortunately, this was not explored further, therefore, it is unknown if this positively resulted in variability within a task or variation of tasks. This tendency to frequently vary activities within a single session may be attributed to minimising physiotherapist boredom or perceived participant boredom, and/or because physiotherapists do not observe any change in participant performance during sessions. Participants could become fatigued, which may negatively affect their performance of sit to stand or walking during the session but learning (structural plasticity) may still occur that has a positive impact on functional outcomes post-discharge. Thus, it is conceivable that physiotherapists may assume their treatment is not effective and change the task. However, switching from one task to another or changing the context in which the task is practiced can cause interference where learning one motor task interferes with the learning of another similar motor task[428]. Low contextual interference produces superior short-term effects that may be observed within one session, but high contextual interferences results in greater long-term learning effects which are associated with greater generalisability of the practiced tasks to other settings[430].

If physiotherapists are frequently changing activities, this may negatively affect dose and intensity. Whilst there is increasing evidence that high intensity stroke rehabilitation programmes are effective[237,426] these have focussed on the upper limb in people with chronic stroke and were not representative of people with

severe stroke. Given, however, that the 'active ingredients' of neurorehabilitation are not yet known[237], this approach to varying the practice of tasks cannot be supported or refuted.

Finally, the type of feedback provided during the intervention was not standardised. There are two types of feedback in motor learning: response-produced information that is available to learners through their sensory systems both during and because of movement (intrinsic feedback), and augmented feedback, which is information received from an external source, e.g. a physiotherapist's comments, during or after movement. Augmented feedback can play a motivational role in the learning process[428]; therefore, it is possible to surmise that if physiotherapists are not on-board with the intervention they may not motivate and encourage participants; this in turn could negatively affect the participants adherence. Motivation is discussed further in Patient-related factors (5.2 Adherence). Augmented feedback may be required if sources of intrinsic feedback are affected such as sensory loss following a stroke.

In summary, there are several factors that could influence learning during intervention sessions. Many of these factors have been investigated in healthy people learning sport-related or artificial complex motor skills, but not in people with severe stroke during the sub-acute phase. Thus, there is an urgent need for research to investigate the relative importance of scheduling of practice, variation of tasks, whole or part practice, manual guidance and feedback for people with severe stroke.

SPIRES participants experienced a range of impairments and fatigue levels that physiotherapists reported negatively affected participants' ability to undertake the intervention. Despite scepticism that people with stroke could not tolerate high doses of therapy[432], participants in two studies were able tolerate and

complete either 300 hours over 12 weeks[426] or 90 hours[237] over three weeks despite severe upper limb disability and a range of impairments and fatigue levels. In SPIRES, some physiotherapists shared this scepticism, suggesting the intervention was not suitable for people with very severe stroke, and stating they would prefer a shorter duration (e.g. two weeks instead of three) or less sessions per week, with only a few physiotherapists acknowledging the impact this would have on intensity.

Eight to 12 repetitions of sit to stand were recommended in SPIRES (see Chapter 3, Section 3.8 for justification). However, in recent years, evidence that higher intensity of up to 300 repititions[433] has demonstrated greater improvement, although these have been for the upper limb and not with people with severe stroke. Thus, the minimal number of sit to stand repetitions in people with severe stroke required for improved outcomes, and the maximum number of repetitions that someone with severe stroke can achieve remains unknown[103]. SPIRES participants achieved a mean of 4.64 (±3.9 SD), median 3.00, range 0-20 sit to stand repetitions. Recommendations for a future definitive trial could be based on available evidence that a minimum number of 10 repetitions are required and investigate the impact of severity on the achievable graded percentage increase per session and maximum number repetitions achieved.

In a definitive main trial, it is suggested that more emphasis should be placed on the importance of undertaking the sit to stand repetitions within the training sessions.

6.8 OH protocol

The data from the interviews and focus group indicated that the physiotherapists did not consider monitoring BP when standing patients as part of their usual clinical practice. Instead, they judged the presence of OH based on clinical symptoms and appeared surprised that participants who were asymptomatic had a significant drop in BP. The literature, however, suggests that most patients with OH are asymptomatic or have few non-specific symptoms[434], which highlights the importance of assessing and monitoring OH in SPIRES and other stroke rehabilitation trials involving standing. However, the prevalence of OH in SPIRES was lower than anticipated. During the minimisation process 15.6% (n=7) of participants experienced OH, compared with 20% (n=9) during the intervention period, which is not as high as the 52%[109] as previously reported in the systematic review (Chapter 2). This small difference in the prevalence of OH at the point of minimisation compared to the intervention period, suggests the screening process of lying to sitting was adequate and appropriate for implementation in a definitive main trial. However, the knowledge and skills (ability to measure BP manually) of physiotherapists about the importance of measuring BP when undertaking standing interventions in this patient group needs to be considered.

The work instruction for the intervention stated blood pressure (BP) needed to be monitored for the first three sessions, and once BP was within the participants' normal range for three consecutive sessions, monitoring was no longer required. Some physiotherapists reported that taking manual BP with people with very severe stroke was challenging in terms of the time, number of staff required to assist participants into standing and take the BP, as well as monitoring the participant's position in the standing frame. Experience of using

the standing frame and taking manual BP varied which may have affected efficiency, confidence and competence of the task. For example, at one site I needed to provide training on how to manually measure BP and to facilitate patients in and out of the frame. Level of experience and training in the procedure and interpretation of manual BP measurement, as well as environmental factors and patient factors (e.g. medications, anxiety, time of day etc.) may affect the reading[435,436]. Thus, lack of time, experience and staff may have affected the consistency and accuracy of measurement.

In summary, in light of the evidence from the literature regarding the risk of harm from OH in people in the sub-acute phase of stroke (discussed in chapter 2), and the challenges faced by the physiotherapists in undertaking BP measurement in this feasibility trial, it is therefore recommended that a definitive main trial should include training on BP monitoring and its interpretation, emphasising the potential risk of harm by not adhering to the OH protocol. Additionally, medical staff should be involved in the training to enable them to provide pharmacological interventions as and when required.

The systematic review (Chapter 2) was completed after recruitment had closed, thus other non-pharmacological interventions deemed effective in treating OH are now known and can be incorporated into a definitive main trial. This will provide therapists with other options (e.g. electrical stimulation, physical manoeuvres, lower limb compression stockings/bandages) when an abdominal binder is contra-indicated, such as percutaneous endoscopic gastrostomy. Thus, the OH protocol needs to be further developed prior to moving forward with a definitive main trial, which would potentially include determining the effectiveness of the revised OH protocol.

6.9 Outcome measures

The feasibility of the proposed outcome measures was evaluated by determining the percentage completion of the primary and secondary outcome measures. Their ability to detect change in this sample of severe stroke was also explored.

Proposed primary outcome measures

The feasibility and acceptability to participants/proxies and blinded assessors of two primary outcome measures were determined: the Barthel Index (BI)[275] and Edmans[279]. Completion of both primary outcome measures was 100% at baseline and, with exception of the participants who withdrew, all but one participant completed their primary outcome measures at all timepoints. Cognitive and/or communication impairment affected some participants' ability to self-report for both proposed primary outcome measures, therefore a proxy was used (clinician, relative or carer). The proportion of participant and proxy responses were similar at all time-points: 19 participants (42.2%) at baseline and 22 participants (48.9%) at 55 weeks.

Proxy responses are an important alternative to source information when participants have cognitive and/or communication impairment that prevent them from answering questions in clinical trials. However, disagreement between proxy and patient responses may introduce measurement error and bias into trial results[437]. For instance, proxy respondents may under- or overestimate the functional status of the patient, and of particular relevance to the SPIRES trial, agreement between proxy and patient responses are lowest for patients with more severe strokes[438]. In acute stroke, disagreement is worse at initial administration, suggesting the need for an adjustment period or “learning curve” for proxy respondents and/or patients[439].

The use of proxy responses for the Edmans ADL Index for Stroke has not been studied. Although wide limits of agreement between patient and proxy responses for the BI have been reported, nevertheless, the use of proxy responses with this measure is supported for clinical research[440]. Patient and proxy responses should not be used interchangeably to monitor patients because of the wide limits of agreement between the two responses. Therefore, it is recommended that for a SPIRES definitive main trial, proxy and self-report will be collected. It is acknowledged that this will increase the amount of time required for the assessment, however, if only one outcome measure of functional activity is subsequently used (see below) it is reasonable to presume that this will be both acceptable and feasible.

Whilst the focus of this feasibility trial was to test the procedures of the outcome measures and determine feasibility and acceptability[238], it also afforded an opportunity to explore if the proposed outcome measures were responsive to change in people with severe stroke from a sub-acute to chronic stage (12 months). Both the BI and Edmans ADL Index for Stroke showed similar magnitude of improvement in scores at each time-point across the course of the trial. Both were able to distinguish between control and intervention groups, suggesting they were appropriate measures. Responsiveness of a scale/measure refers to the ability to detect change, which is an important quality for assessing treatment effectiveness[441]. However, caution needs to be applied when looking at responsiveness over time in SPIRES because this feasibility trial is not adequately powered. Thus, it is important to review the existing literature for these two measures. The original study suggested that the Edmans ADL Index for Stroke was responsive to change, however, this was only measured during admission and discharge, the duration of which was not

reported[279]. Additionally, they did not provide data on severity of stroke, therefore, it's responsiveness in people with severe stroke is unknown. The BI has demonstrated a limited ability to detect change at extremes of ability, making it less discriminating in severe stroke[278] but is recommended for use during the sub-acute phase.

The minimal clinically important difference (MCID) also warrants discussion. This is the smallest meaningful change in score considered clinically important as reflected by a meaningful and beneficial change in health status perceived by the patient[442,443]. There is no MCID data on the Edmans ADL Index for Stroke. For the BI, a MCID of 1.85 points has been deemed clinically relevant in people with stroke even if the change score has not reached statistical significance (P> .05)[444]. In SPIRES a mean of 2 to 3-point increases in BI scores were observed between some time-points. Given that this relates to the total summed score, this may have reflected an improvement in a range of different items such as walking, regaining continence or being able to wash and dress independently. Notable, however, is the evidence which suggests that the BI is less able to measure change in people with severe disability[278], which may result in underestimation of treatment-induced changes and will need to be considered in both the design and analysis phases of a definitive main trial.

There is a paucity of data on the Edmans ADL Index for Stroke, which makes meaningful comparisons with other rehabilitation trials difficult. Given the BI is used extensively in stroke trials[277], despite the aforementioned limitations, using it in a SPIRES definitive main trial would enable meaningful comparisons or meta-analysis with other stroke rehabilitation trials.

Proposed secondary outcome measures

Several proposed physical secondary outcome measures were used: knee extensor strength, joint range of movement using goniometry, modified Ashworth Scale, Trunk Control Test, the rationale for which are detailed in Section 3.12, Chapter 3. This feasibility trial demonstrated that administration of these measures was both feasible and acceptable to participants and blinded assessors in this sample of people with severe stroke.

The battery of tests were chosen to reflect the secondary neuromuscular impairments commonly observed post-stroke, which the intervention aimed to minimise (Chapter 1, Section 1.2). The Trunk Control Test was selected because trunk control is strongly correlated to common daily functional activities such as the ability to sit, sit to stand and walk[284]. In SPIRES it was able to detect change over time both within and between the groups, however, in some participants a ceiling effect was observed. Therefore, exploration of an alternative measure is warranted prior to progressing to a definitive main trial. Physiotherapists identified the modified Rivermead Mobility Index (MRMI) as a possible replacement during the focus group when discussing eligibility criteria. The MRMI consists of eight tasks related to mobility in the acute stroke patient: turning over in bed, lying to sitting, sitting balance, sit to stand, standing, transfers, walking and stairs[445]. There is a total possible score of 40, with higher scores indicating better mobility, and each individual task is scored from 0 (‘unable to perform’) to 5 (‘independent’). The wide range of activities would allow for variation of progression throughout the duration of the trial. Given the functional standing frame programme incorporates standing and sit to stand, a measure that incorporates this and the elements of trunk control seems

appropriate. It takes 15 minutes to administer[446] which does not appear overly burdensome.

It is essential to target outcomes that are important and relevant to patients and clinicians[447]. Patient and public involvement informed the selection of outcome measures used in SPIRES. However, most of the outcome measures used, including the patient-reported outcome measures (PROMs) were developed several years ago, some over ten years ago[271,273,275,296,448,449] and may not have involved patients and clinicians in their development. It is possible therefore that there is a mismatch between the priorities of people with severe stroke, clinicians and current stroke services. For example, the length of stay has substantially reduced with greater emphasis placed on community rehabilitation, thus patients' priorities in terms of outcomes may change depending on the stage of their stroke rehabilitation continuum.

In stroke rehabilitation there is no standardised recommendations for outcome measures. The Stroke Recovery and Rehabilitation Round Table[411], consisting of researchers and clinicians, has generated consensus recommendations for core data collection across sensorimotor stroke rehabilitation trials, which recommends the 10-metre walk test. However, this measure is not appropriate for the target population of this trial, people who are unable to walk early post-stroke.

The absence of standardisation of outcomes makes pooling results from rehabilitation trials and producing meaningful comparisons difficult. Recently a mixed-methods study identified that post-stroke rehabilitation research would benefit from a reduction in the number of outcome measures currently used, and better alignment between what is measured and what is important to stroke survivors, carers and clinicians[450]. Unfortunately, this study only looked at arm

outcome measures, but they did include PROMs. Future research needs to investigate this in lower limb, gait and mobility outcome measures, ensuring inclusion of all stroke severities.

6.10 Patient-reported outcome measures

PROMs are standardised, validated questionnaires completed by the patient to determine their perceptions of their health status, level of impairment, disability, and health-related quality of life[451]. In stroke rehabilitation trials of early standing, PROMs have not been consistently used. Instead, clinician-reported outcome measures have been used[274,278], which has the limitation of not capturing the impact on a patient's quality of life. However, PROMs require the patient to be able to comprehend the question and express a response. An objective of this feasibility trial was therefore to evaluate the ability of people with severe stroke (who may have moderate to severe cognitive and communication impairments) to complete the PHQ-9[289], SAQoL-39[295] and EQ-5D-5L[296] self-report measures.

This feasibility trial demonstrated that communication and cognitive impairments affected participants ability to complete the PROMs. When comparing the two health-related quality of life (HRQoL) questionnaires, at baseline more participants were able to complete the multiple-choice questions for EQ-5D-5L (86.7%) than the SAQoL-39 (75.6%). However, only 77.8% were able to complete the health state for the EQ-5D-5L, which required participants to score their health out of 100. Ability to assign a rating can be affected post-stroke due to reduced capacity of abstract thinking[452] as well as ability to write, point to or speak their response, but completion rate was higher than the SAQoL-39.

In terms of feasibility and acceptability of these two measures for both participants and assessors, the EQ-5D-5L had several advantages. The EQ-5D-5L has five questions, plus rating overall health status out of 100, compared to 39 questions for the SAQoL-39. The blinded assessors perceived the SAQoL-39 took too long to administer, asked too many questions, and was not appropriate for people with severe stroke. The SAQoL-39 was developed specifically for people with (mild to moderate) aphasia and has shown good reliability, validity and responsiveness for change in these individuals[454]; the authors acknowledge it is not suitable for people with severe aphasia. Severe physical and/or cognitive deficits may also affect completion of measures of this nature. The authors do not appear to have acknowledged the impact of the length of the questionnaire on fatigue.

Cognitive impairment, specifically anosognosia, also affected completion of the PROMs in this feasibility trial. Anosognosia is a self-awareness disorder that prevents people with brain damage from recognising the presence or appreciating the severity of deficits in sensory, perceptual, motor, behavioural or cognitive functioning, which are evident to clinicians and caregivers[454,455]. This can impact on an individual's ability to report their experience of stroke accurately, by systematically overestimating their abilities[452]. Difficulty in reporting the degree of disability, distress or impairment accurately due to anosognosia affects the validity of PROMs yet is rarely discussed or addressed either in clinical practice or clinical trials[455]. Anosognosia was identified in four participants by the SPIRES Chief Investigator, but there was no formal screening. Screening for anosognosia and other neuropsychological deficits such as spatial neglect, abnormal magnitude estimation and deficits affecting semantics and abstraction[452] may have identified a higher prevalence. At

present no single scale can fully explore all the components of anosognosia and development of a scale for use in stroke to address the potential threat to validity with PROMs has been identified as a priority for future research[452,456]. This will be explored further prior to progressing to a definitive main trial.

SPIRES participants reported they did not mind answering the PROM questions, did not find them intrusive, and were willing to answer any questions if it was going to help them or someone else.

Not all participants could read and self-complete the PROMS and hence needed assistance form the blinded assessor to do so. One blinded assessor reported to feeling uncomfortable when asking some questions, especially with the PHQ-9 because some participants became tearful. They felt it was challenging to ask these questions when they had not had the opportunity to build up a rapport with the participant. The blinded assessor also reported that the questions in most of the PROMS drew attention to what participants found challenging/impossible to do. Of interest, this concern was not expressed by any of the stroke participants.

In summary, it proved feasible within this feasibility trial to collect data using the EQ-5D-5L with people with severe stroke, whereas this was not the case for all the PROMS. It is therefore anticipated that the EQ-5D-5L will be the only PROM used in a definitive main trial, which mirrors the recommendations of the Stroke Recovery and Rehabilitation Roundtable[411]. This has the advantage that it will enable a health economic analysis to be conducted, which will be briefly discussed in the future directions section.

6.11 Training

Overall, 50 physiotherapists, occupational therapists, speech and language therapists, therapy support workers, research nurses and research therapists received training across the four sites. Training consisted of an overview of the trial (background, rationale, aims and objectives, design) and trial processes and procedures (research governance, Work Instruction and documentation). All staff completed their GCP training separately. The experience of implementing this feasibility trial is that additional training is required for a definitive main trial to optimise clinical and personal equipoise (discussed in Section 5.5).

A range of barriers have been identified in relation to implementing the intervention and trial processes, many of which could be facilitated with training. Training has been identified as both a barrier and facilitator to trial success[412], however there are no recommendations as to what comprises effective training. This is largely attributed to the heterogeneity of trial interventions. However, commonality exists in the barriers to trial success that could enable a core set of standards for training in stroke rehabilitation trials to be developed, which would facilitate recruitment, retention and intervention fidelity. Common themes such as clinical and personal equipoise, gatekeeping, the impact of clinicians' beliefs and attitudes and unconscious bias are relevant in all clinical trials[352,412].

Physiotherapists in SPIRES were keen to share their ideas and experiences with each other and suggested multi-modal training and support would be helpful to implement throughout a definitive main trial. This could include the use of: video clips, vignettes, peer support, online resources, a secure forum to share ideas or ask questions of other treating therapists involved in the trial and more in-depth training prior to commencing recruitment. Web-based training for

treating therapists have been used successfully in other rehabilitation trials, which have effectively delivered information in multimodal learning formats[457]. An advantage of web-based training is that it could keep training costs to a minimum without compromising quality and effectiveness. Clinical vignettes are patient-related cases and scenarios to which clinicians are asked to react. Demonstrated to be effective in healthcare education[458,459], these could be developed to include issues related to adherence, gatekeeping and personal and clinical equipoise. Whilst there is a wealth of evidence showing that peer-support is effective for patients in clinical trials[460,461] there is a paucity of such evidence for training clinicians in clinical trials. Given that peer support is deemed effective in clinical practice because it provides opportunities to learn from others and develops confidence in clinical practice[462], it not unreasonable to propose that it could translate into clinical trials.

Future training should incorporate the perspectives of both physiotherapists and patients to address issues identified with adherence (Section 5.2). It is anticipated that this would primarily be focused on patients' desire to be motivated by their physiotherapist, encouraged to keep working during their sessions and to provide short and frequent rest breaks where appropriate. It could also cover theory on motor learning, task specific training, dose and intensity to reinforce the underpinning mechanism of action of the proposed intervention, thus providing a clear rationale to emphasise the need to adhere to the protocolised intervention. Finally, to stress the clinical relevance of the trial, it is considered important that those engaged in the trial are made aware that the research question originated from clinical practice, and the trial was co-designed with people affected by stroke and multi-disciplinary clinicians involved in management.

In this feasibility trial a Work Instruction was provided with two algorithms, which focused on the intervention procedure, however, this did not include a training protocol detailing any treatment progression. Whilst physiotherapists said they found the Work Instruction helpful it could be improved to include treatment progression as used in other trials[426]. This may positively influence protocol adherence.

6.12 Delivery of national targets and rehabilitation trials

National clinical guidelines for stroke in the UK recommend patients should 'accumulate a least 45 minutes of each appropriate therapy every day at a frequency that enables them to meet their rehabilitation goals'[3][p.25]. The SSNAP monitors therapists' self-reported performance against the guideline target[469]. Published quarterly performance ratings from the SSNAP consistently identifies that therapy frequency and intensity are not met in most stroke units. Data from studies that have analysed the SSNAP data[372] and carried out large and comprehensive mixed-methods case-study evaluation of multiple SRUs[373] , (the ReAcT study) have identified multiple interlinked factors influencing therapy provision, many of which were identified in SPIRES. For example, patient factors such as fatigue and therapists' beliefs about patients' ability to tolerate therapy influenced the amount of therapy patients received. There were differences in the amount of physiotherapy minutes received based on age and stroke severity, with those aged ≥80 years and patients with severe stroke receiving less physiotherapy. This was particularly evident with people with severe stroke when physiotherapists perceived they had limited rehabilitation potential[372]. Given these factors have been highlighted in clinical practice, it is understandable these factors were identified in SPIRES and affected intervention adherence. The ReAcT study[373], a mixed-methods case study

evaluation of eight stroke units, investigated why stroke survivors do not receive recommended amounts of active therapy. Staffing numbers in the ReAcT study[373] were lower than recommended[349] thus meeting the SSNAP targets was challenging. This was mirrored in SPIRES and some physiotherapists identified a tension between meeting the SSNAP target for all patients in the SRU and delivering the required length and number of sessions for SPIRES “it can be quite strenuous if you’ve got four people standing in the frame in a day and you’ve only got two therapists in, being able to meet your stats is difficult” [Physio 5]. If therapists are struggling to deliver the number and duration of sessions recommended in national clinical guidelines[373], it is unsurprising that adherence in SPIRES was low due to the additional demands of the trial and its associated procedures.

SSNAP captures the total number of minutes of therapy received by a patient, however, the content of the session is not recorded and duration of session (minutes) does not necessarily equate to the number of minutes a patient is active during therapy. This was highlighted in the ReAcT trial[373] where therapists reported patients not being ready for scheduled therapy resulted in them spending most of a session assisting the patient with personal care and/or getting out of bed which limited the amount of time left for active therapy. In SPIRES, physiotherapists recorded the duration of standing (minutes), number of sit to stand repetitions and total duration of session (minutes). Some participants completed a 45-minute session and stood for five minutes and performed two sit to stand repetitions. However, therapists were only required to record reasons why sessions were not completed, therefore, it is unknown whether the duration of stand and number of sit to stand repetitions was due to

patient-related, physiotherapist-related or organisational/cultural factors identified in Chapter 5.

Some issues identified with the SSNAP data have also been identified in rehabilitation trials which negatively impacted implementation and contributed to negative outcome. The TRACS (Training Caregivers After Stroke)[470] cluster RCT introduced structured caregiver training in stroke care but this did not demonstrate any benefit. A process evaluation of the trial concluded factors such as short length of stay, discharge driven environment where rehabilitation is a low priority, lack of research culture, competing organisational demands, staffing levels and experience as well as the additional demands of trial participation negatively affected trial implementation and outcome. This aligns with SPIRES where physiotherapists identified the increased workload of trial procedures, for example, some therapists felt completing and photocopying the paperwork “can take up quite a chunk of time” [Physio 3]. Some therapists highlighted the number of therapists needed to facilitate people in to standing “you need quite a lot of hands; sometimes three or four people so it’s obviously just taking other therapists off the ward but that’s the only negative thing about it” [Physio 4]. This links back to the challenges with meeting the SSNAP targets. Therapists in TRACS[470] reported they had ‘very little time to actually do the rehab programme’ and researchers observed therapists over-estimate the number of minutes of therapy they had delivered to patients for the SSNAP data compared with number of minutes they were observed providing therapy. In SPIRES physiotherapists were required to document the number of minutes of standing and the duration of sessions. The duration of all sessions were recorded in five-minute intervals from 5-60 which was not stipulated in the CRFs but standing duration was recorded to the nearest whole minute which was

stipulated in the CRF. However, having to record the number of minutes to the nearest whole minute may have challenged usual working practices and/or led to estimates of standing time that would potentially affect the reliability of the data.

Another stroke rehabilitation trial with a negative outcome was CIRCIT (Circuit class therapy or seven-day week therapy for Increasing Rehabilitation Intensity of Therapy after stroke)[471]. Delivered in inpatient sub-acute SRU's, participants were between 5 and 197 days (mean of 28 days) post-stroke and randomly assigned to usual care therapy five days per week, usual care therapy seven days per week, or circuit class therapy five days per week. The primary outcome was the 6-minute walk test at four weeks post-randomisation. Despite a substantial increase in therapy time (three hours over four weeks for seven-day participants and 22 hours over four-weeks for circuit class participants) there were no differences in outcome between groups. Authors concluded the content of therapy sessions, e.g. what participants did during therapy time, was a likely factor in the negative outcome. Observational data (published separately) from sessions to measure fidelity[472] identified that participants spent a large proportion of time resting and therapists underestimated rest time by 36% and overestimated active therapy time by 28%. The authors suggest that one of the reasons therapy dosage studies have shown small effect sizes may be that many have relied on therapist estimations of therapy time. Given the low number of sessions observed for fidelity in SPIRES, it is not known if therapists over or under-estimated time in therapy (in both groups) or time in standing or sit to stand repetitions in the intervention group.

The outcomes of large rehabilitation trials[470,471] and SPIRES feasibility trial highlights the challenges of delivering trials using existing staff and resources.

Data from observational trials[373] have identified multiple interlinked factors influencing therapy provision, and it has been suggested that aspirational trials[237,473] are needed with additional rehabilitation resources and different service delivery models. However, addressing the impact of adherence and how that is affected by beliefs of therapists and patients and organisational/cultural factors is also required to optimise the delivery of evidence-based practice as well as optimising the outcome of future rehabilitation trials.

6.13 Clinician-researcher reflections

I have been a physiotherapist for 12 years but being Chief Investigator for SPIRES gave me a new role: clinician-researcher. A clinician-researcher is an individual who conducts research and provides direct patient care[463] although not at the same time or for the same organisations. It is important to acknowledge the potential benefits, challenges, barriers and facilitators of this dual role as well as the dual-perspectives and associated boundaries and what impact it can have on my research.

I identified tension between my role as a physiotherapist and a researcher. During the follow-up visits some relatives and participants had expectations of my visit. For instance, several relatives made assumptions that I was there to provide physiotherapy or that I could influence access to physiotherapy or other healthcare professionals and services. I acknowledge there is a potential that my role as a physiotherapist may influence their decision to grant me access for the follow-up visits. On several occasions in participants' place of residence, relatives and staff requested my professional opinion about the participant's environment, safety and absence of physiotherapy. Some participants also asked for my professional opinion about their rehabilitation. I felt there was role confusion and the relatives and participants were unable to distinguish my

clinical and research roles which is not uncommon in clinician-researcher roles[464]. I clarified my role, explaining the purpose of my visits, and signposted staff and relatives to members of the participants' usual clinical care team. On three occasions I contacted General Practitioners and a physiotherapist to report falls and request a review due to development of secondary neuromuscular impairments that warranted urgent intervention. This prompted me to change how I introduced myself on the telephone when arranging follow-up visits. Instead of stating that I was a physiotherapist researcher, I said that I was a researcher therapist which reduced role confusion.

I also acknowledge how my role as physiotherapist-researcher may have affected recruitment at my local site. I worked at Site 1 for eight years and was familiar with many of the staff, therefore, treating therapists may have wanted to support me on a personal level by supporting the trial. Additionally, because I lived locally to this site, I was able to drop in and catch-up with the treating physiotherapists and ask about recruitment and admissions.

6.14 Future directions

The results of this feasibility trial and the discussion chapter have highlighted issues that need to be addressed prior to progressing to a definitive RCT. Some of these are modifiable and some are not, highlighted in Figure 6.2 and summarised in Table 5.1.

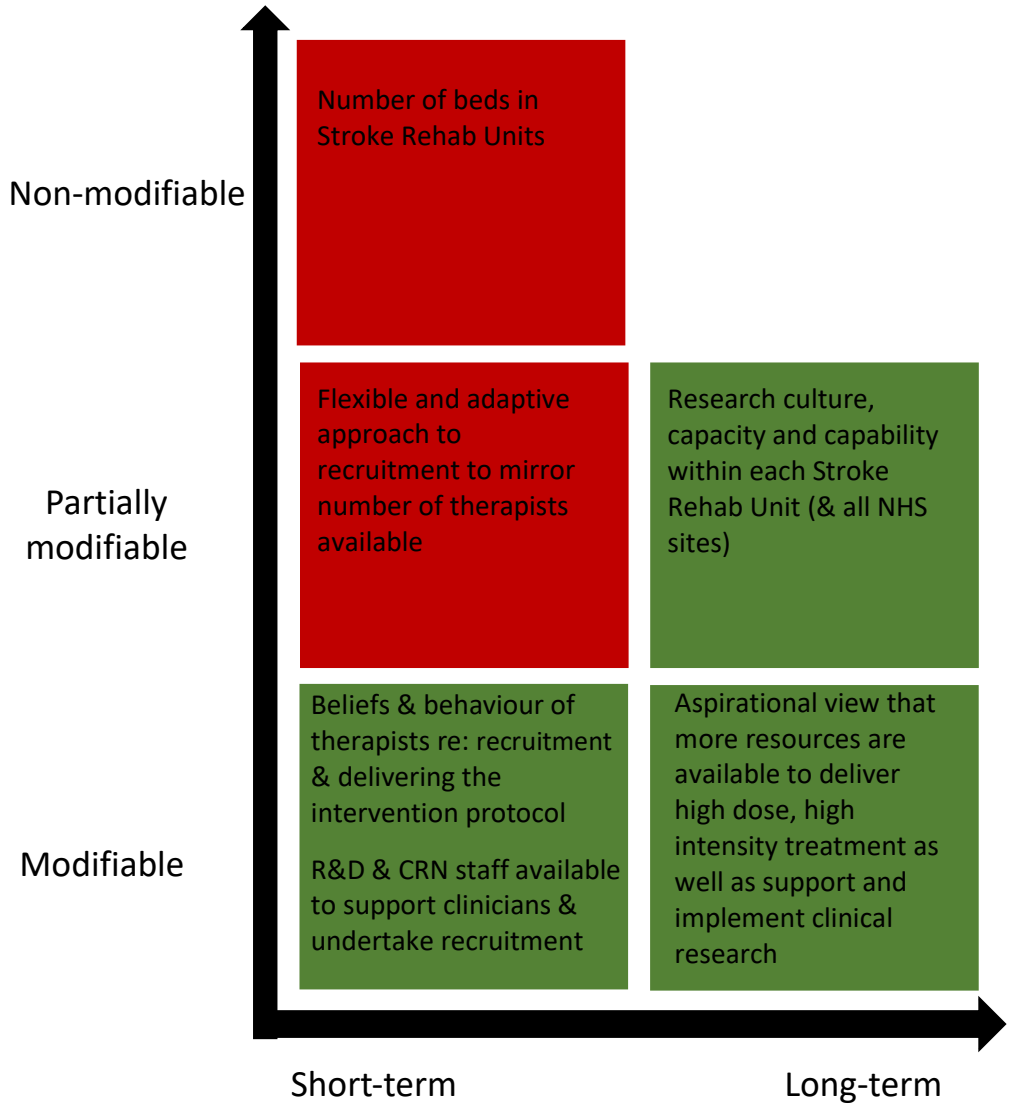


Figure 6.2 Modifiable and non-modifiable factors

Activity	Lessons learned /challenges faced	Recommendations for a definitive trial
Intervention		
Protocolisation of the intervention	A detailed prescription of starting position of sit to stand repetitions was not provided in the protocol, which participants performing sit to stand for a standard seat height. This may be too challenging for people with severe or very severe stroke and may have attributed to the low number of repetitions during sessions. The qualitative and quantitative data suggest that some physiotherapists were not invested in the intervention or the intervention did not align with their beliefs and preferences for treating people with severe stroke. This combined with competing priorities resulted in low adherence of the intervention protocol.	Optimise standardisation of the intervention by prescribing the starting position, e.g. perch sitting, raised seat height, natural position and progression would include lowering and varying seat heights. This could be incorporated into video resources that would provide physiotherapists with protocolised procedures as well as hints and tips from physiotherapists who have been through the feasibility trial. This could include ways of progressing participants and activities that can be undertaken in the frame, as well as outside the frame for those who progress to walking. Future training for SPIRES would incorporate clinical and personal equipoise, subconscious bias (including belief system) as well as rehabilitation potential, paternalism and intervention fidelity. Additionally, use data from patient participants to highlight the different perspectives and emphasise that although patient participants were tired, they are reliant on their physiotherapist to motivate and encourage them. Pre-hoc, investigate adherence to identify facilitators.
Overall adherence to the intervention	Criteria for overall adherence (total standing duration and sit to stand repetitions over the 3-week intervention) did not incorporate a graded increase of sit to stand repetitions and standing time per week to allow progression over time. Thus, participants were expected to achieve 100% adherence.	Pre-hoc, define adherence for each of the three weeks in terms of sit to stand repetitions and standing duration. Consider different criteria for participants with moderately severe (mRS 4) and very severe (mRS 5), e.g. able to achieve placed sitting balance for 10 seconds or sitting balance with minimal assistance of one person. Set adherence for each element of the standing intervention, e.g. participants should achieve 80% of the standing duration either each individual session or number of minutes in total per week, and 80% of sit to stand repetitions per session/or total per week. Incorporate information gained from the qualitative data from patient participants regarding their need to be pushed through the

		tiredness/fatigue in pre-trial training of physiotherapists delivering the intervention. Also incorporate into the training that this trial evolved from a physiotherapist working with people with severe stroke who identified the lack of opportunities to stand and increase intensity of practice, and it was co-designed with physiotherapists and occupational therapists working in stroke rehabilitation units and with people with stroke and their relatives. Monitor adherence closely through a definitive trial and address any issues as they arise. Consider implementing stopping rules related to adherence. Additionally, consider a run-in period where participants receive the functional standing frame programme to provide information on treatment adherence. The purpose would be to identify poor adherence, or uncooperative attitudes and behaviours that can be addressed at the time[465]. Increase the frequency of fidelity monitoring and analyse data regularly and address any training or logistical issues in a timely manner. Review the data from the 100 reps a day by Stroke Education Collaboration[466] which could be incorporated for those with mRS 4 and/or those that progress to standing outside the frame. Determine the minimum number of sit to stand repetitions required to improve outcome and the maximum number of repetitions someone with moderately severe and very severe stroke can achieve. Consider undertaking ethnographic research or using case studies with trial participants, physiotherapists from the trial and other clinical trialists exploring adherence of both physiotherapists and patients in depth.
Trial procedures		
Minimisation and stratification	There was a higher prevalence of total anterior circulatory stroke (TACS) in the intervention group and partial anterior circulatory stroke (PACS) in the control group. TACS is typically associated with	Stratify for stroke classification for definitive trial to balance groups for this variable.

	greatest severity and worse outcome, PACS the highest risk of recurrence, whilst LACS has the mildest severity, and POCS the most favourable outcome[467].	
	Pre-stroke disability varied between groups, with more participants classified as mRS 4 in the intervention group (22.7%) compared to the control group (13.0%).	Consider stratifying for pre-stroke disability, although this may link with the proposed inclusion of a pre-stroke frailty score.
Measuring OH	The method used in the minimisation procedure did not accurately assess OH as indicated by the higher prevalence of OH detected during the intervention sessions.	Incorporate standing into the assessment of OH for a future trial, using a tilt table or standing frame.
OH Protocol	The systematic review (Chapter 2) was completed after recruitment had closed. However, an OH protocol was developed in collaboration doctors and therapists and literature from the review which resulted in compression garments (abdominal binders) being used for participants with OH. Thus, other non-pharmacological interventions deemed effective in treating OH are now known and can be incorporated into a definitive main trial.	Pre-hoc, develop the OH protocol algorithm which would potentially include determining the effectiveness of the OH protocol in a definitive main trial.
Fatigue	Given the high prevalence of fatigue (82% scoring 4-10 on a visual analogue scale out of 10), a systematic review of interventions to manage fatigue may have facilitated greater adherence.	Pre-hoc, a systematic review of interventions to treat fatigue is warranted.
Foot sensors	Despite several iterations in the design and manufacture, physiotherapists deemed them unreliable and	Further development with physiotherapists and people with stroke if they are to be used in a definitive main trial.

	temperamental and were not convinced participants liked them.	
Recruitment	Selection bias and paternalism was identified in this feasibility trial and this has the potential to negatively affect recruitment.	Unconscious bias and paternalism should form part of the training for a future definitive trial. Vignettes could be used to aid learning. Additionally, Research and Development or Clinical Research Network staff would identify and screen potentially eligible participants. This would alleviate any ethical dilemmas for therapies or missed opportunities for recruitment
	Reduced staffing negatively affected recruitment.	A flexible recruitment rate allowing the recruitment rate to reflect the number therapists employed. Furthermore, sites would need to have ≥15 beds as there are likely to be a higher number of physiotherapists due to ratios of staff per bed.
	Research culture within each of the four sites varied which affected recruitment of participants into the trial and adherence to the trial protocol.	It is acknowledged that a cultural shift may take time to modify, however, training as part of a definitive trial could facilitate a bottom-up approach to therapists building a research culture within their site.
Outcome measures		
Ability of participants to complete PROMs	Ability to complete PROMs improved over time which resulted in switching between proxy and participant responses, e.g. changing from SADQ-10 to PHQ-9 at different assessment time points which may affect the validity of the results. The SAQoL-39 was deemed too long by blinded assessors and less participants (75.6%) completed the SAQoL-39 compared to the EQ-5D-5L (86.7%). Furthermore, the EQ-5D-5L has a question on anxiety and depression which perhaps negates the need for a separate measure for mood.	Capture both self-report and proxy responses at all time points in a future definitive trial for participants who can self-report at baseline. The EQ-5D-5L will be the only PROM used in a definitive main trial, which mirrors the recommendations of the Stroke Recovery and Rehabilitation Roundtable

Completion of the outcome measures	Cognitive impairments such as anosognosia affected completion of PROMs, which may make it impossible for people with this condition to report their experience of stroke accurately due to systematically overestimating their abilities, which has been identified as a confounding influence on PROMS	Screen for anosognosia at baseline, although. However, there is a paucity of evidence on this topic which necessitates development of a screening tool specifically for anosognosia prior to a definite trial Pre-hoc, consider whether PROMs are appropriate for people with severe stroke to complete, and whether observational measures would be more appropriate for the definitive trial.
Participant versus proxy responses	The number of proxy responses reduced over time for the proposed primary outcome measures; switching from proxy to participant may affect the scores due to the potentially different perspectives of those completing the questionnaires. This may result in over- and or under-estimations of competency in the domains depending on who completes the questionnaire.	Consider consistency of proxy responses across all time points. Considerations should also be made to the availability of the same proxy across all time points, which may be particularly challenging for participants who live alone, and the proxy is a paid carer (e.g. availability and consistency of staff)
Evaluation of quality of life	Lower completion rates of the SAQoL-39 than the EQ-5D-5L occurred. Qualitative data from the PI and CI's field notes suggest the SAQoL-39 would not be suitable for a definitive trial. Although it was devised for people with aphasia, it was not able to be used by participants with moderately severe or severe aphasia or participants with cognitive impairment.	Use the EQ-5D-5L as the measure of quality of life, which will have the additional benefit of being utilised in a health economic evaluation.
Design		
Individual participant versus site randomisation	Physiotherapists wanted to experience delivering both intervention and control conditions, but a cluster RCT would avoid treatment group contamination and may enhance adherence with increased fidelity and resources.	A factorial stepped-wedge cluster RCT should be considered. This would provide the opportunity to determine the clinical and cost-effectiveness of SPIRES intervention at two timepoints: inpatient sub-acute stroke rehabilitation (early) and the community (late).

Duration of intervention period	Opinions varied among physiotherapists as to the ideal intervention duration and this appeared to be influenced by organisational factors. Additionally, the national average length of stay has reduced since this feasibility trial was designed.	This links to the point above re the factorial stepped-wedge RCT. Future work should aim to collaborate with a consensus group/expert panel to determine the future trial design including duration.
Dose and intensity	Evidence suggests that increased frequency and intensity of therapy leads to better outcomes but the dose and intensity of SPIRES was not achieved by most participants.	Post-hoc, review evidence from Stroke Education Collaboration[466] and other high intensity rehabilitation trials with PPI to determine how intensity could be incorporated into a definitive main trial. This could also be incorporated into the suggested run-in period
Participant (dis)ability	Some physiotherapists were concerned that participants without head or trunk control were “too impaired” for the functional standing frame programme and this appeared to affect recruitment (selection bias).	Participants could start their intervention on the tilt table; which would address physiotherapists’ concerns about manual handling, resources and equity of care. This could be part of the run-in period
Mortality	Twenty-seven participants enrolled in the trial were aged ≥ 80 years, and 11 of the 12 participants who died were aged ≥80 years. An increased risk of mortality is associated with age ≥ 80 years. However, there was very little difference between the number of deaths between groups. Frailty is associated with ageing and some participants may have been classified as frail pre-stroke, which could have increased their mortality risk.	This trial did not use a frailty score therefore, a definitive main trial could include pre-stroke and post-stroke frailty measures which could help identify individuals at the greatest risk of mortality.

Table 5.1 Lessons learned, challenges faced and recommendations for a definitive randomised controlled trial

6.14.1 Future additional studies for people with severe stroke

From this thesis it is evident we are still unclear who can recover post-stroke and the optimal dose and intensity in severe stroke. These are areas that could be subject to separate future studies.

Predictive modelling

As highlighted in this discussion chapter, the trial has identified further areas that could be researched outside of the proposed RCT.

Some participants in SPIRES demonstrated functional recovery and returned to walking and independence in ADLs. Accurately predicting functional recovery and outcome following stroke for the lower limb (balance and mobility) would enable realistic goal setting, guide the type and duration of rehabilitation and help to manage expectations[133]. There is a paucity of evidence for predicting recovery of standing and walking in people with severe stroke (as discussed in Chapter 1 Section 1.3). Existing literature suggests that stroke severity and age have consistently emerged as powerful predictors[134,135]. However, ability and duration of standing following severe stroke is affected by OH and fatigue, thus these factors need to also be considered in any predictive model. Future research needs to develop a predictive model for the lower limb that includes balance and mobility, and has sufficient number of people with mild, moderate and severe stroke to make meaningful predictions to people with all stroke severities. A consensus group should utilise current available evidence on physiological changes post-stroke to develop a predictive model that is applicable for people with severe stroke and testable.

Dose and intensity in severe stroke

High dose and high intensity is deemed effective for people with stroke however, this has focussed on upper limb rehabilitation. There is an urgent need to research high dose and high intensity in rehabilitation of the lower limbs that stratify for stroke severity and include people with mild, moderate and severe stroke to make meaningful recommendations.

There is very little evidence of the impact findings from motor relearning literature on the recovery of people with stroke, and none in severe stroke. Therefore, future research during sub-acute stroke rehabilitation needs to investigate the relative importance of scheduling of practice, variation of tasks, manual guidance and feedback for people with severe stroke, as discussed in Section 5.7

6.15 Limitations and contributions to knowledge, clinical practice and theory

Limitations

The primary limitation of this feasibility trial was the absence of weekly graded adherence criteria over the three-week intervention. Further, fidelity checking was not as frequent as it could have been and was undertaken by different independent assessors. If fidelity checking was undertaken more frequently and the data analysed by one person, this may have provided the opportunity to conduct more training and address adherence. This will be implemented in a definitive trial and should be included in future feasibility trials of complex interventions.

The delay in completing the systematic review resulted in the recommendations from the review not directly informing the non-pharmacological interventions to treat OH protocol used in the trial. However, people with stroke may likely have

impaired swallow (limiting the ability to use drinking water to address OH and already wear pneumatic compression stockings. Therefore, abdominal binders were pragmatically used in the trial OH protocol and their use was supported by the systematic review. However, the OH protocol will need further development prior to implementing in a definitive trial including other potential interventions depending on patient presentation/ability. The absence of a systematic review on interventions to treat post-stroke fatigue has been identified, given the high prevalence of fatigue among participants in the trial. However, the high prevalence was not known until the data was available after the last participant had completed their 55-week follow-up assessment, therefore, a systematic review on post-stroke fatigue interventions is recommended prior to progressing to a definitive trial.

The small sample size of 50 participants is acknowledged as a limitation, as is not recruiting to target. However, 45 participants were recruited in ten months thus the actual monthly recruitment rate exceeded the target recruitment rate.

All SRUs were in the South West of England, therefore, behaviour and attitudes of physiotherapists, patients and relatives are not representative of all SRUs. However, the Proximal Similarity Model used by AVERT trialists[468] considers the person, place, setting and practice and literature reviewed for the discussion chapter in this thesis regarding therapists' beliefs, organisation and patient factors have been identified in other trials nationally and internationally.

A feasibility trial has been conducted; it has not determined if the intervention is clinically and cost effective. This will be the aim of the definitive trial.

6.16 Original contributions to:

Knowledge

The thesis determined the feasibility of a novel combination of two existing physiotherapy treatments: prolonged standing and sit to stand repetitions (task specific training) (Chapter 1).

Several non-pharmacological interventions exist to treat OH in people with stroke and neurological conditions (Chapter 2). There are treatment options available for people with mild, moderate and severe stroke and some of the equipment for these interventions are already available in SRUs, e.g. microstim for electrical stimulation and cycle ergometers.

It is possible to include people with severe stroke who have communication and cognitive impairments in rehabilitation trials.

Beliefs and behaviours of physiotherapists can affect success of a trial, e.g. fidelity

Whilst GCP training was a requirement from NHS Trusts and the trial Sponsor, it does not sufficiently cover aspects of clinical/personal equipoise and fidelity. Many of the barriers identified in this thesis have been identified in other rehabilitation trials (Chapter 6), therefore a training template is required for rehabilitation trials to optimise success.

Clinical practice

It is feasible for people with sub-acute severe stroke to undertake a functional standing frame programme of sit to stand repetitions and prolonged standing although adherence was low (Chapters 4, 5 and 6). Taking manual blood pressures is not part of physiotherapist core skills and some physiotherapists

did not understand the importance of checking blood pressure in sitting and standing when delivering the functional standing frame programme. This may cause harm to people with stroke due cerebral hypoperfusion (Chapters 2 and 6).

Anosognosia is a common phenomenon post-stroke but is not routinely screened for in clinical practice or in clinical trials. Assessment and treatment of this condition is required as it may affect the validity of using PROMs. (Chapter 6).

There is a disconnect between some physiotherapists and patients regarding what patients' abilities are following severe sub-acute stroke and the most appropriate treatment interventions which should be offered to people with severe sub-acute stroke (Chapters 4 and 5).

Theory

The feasibility trial did not aim to generate theory; the aim was to determine if it was feasible for people with severe sub-acute stroke to undertake a functional standing frame programme. However, it has highlighted how physiotherapists are engaging with evidence-based treatment and research and factors affecting this. There is a potential that years in practice versus education or banding may affect engagement with literature and delivery of stroke rehabilitation in SRUs.

Research culture is not embedded in all NHS settings and needs addressing as this affects the success of clinical trials.

6.17 Thesis conclusions

This thesis has been driven by my clinical practice and interactions with people with severe stroke. The thesis has highlighted practical issues of undertaking research within the NHS, in a discharge driven environment. The qualitative

work with patients and physiotherapists highlighted different perspectives of practicalities and complexities of providing rehabilitation for people with severe and very severe stroke. It has also highlighted issues with the SSNAP data in clinical practice, whereby delivering a rehabilitation trial when resources are challenging increases workload and negatively impacts on the success of the trial.

There are several unknowns that need addressing prior to progressing to a definitive main trial, such as contamination. Risk of contamination was identified as a potential problem in the feasibility RCT where individuals allocated to the control group may inadvertently receive some aspects of the standing frame intervention as physiotherapists at each of the sites were treating participants in both groups. There was evidence of possible contamination because physiotherapists reported that delivering the intervention challenged their practice, prompting them to reduce the amount of rest times, and increase active movements and time in standing during treatment sessions.

Recent rehabilitation trials conducted early post-stroke[470,471] and observational data[373] identified issues affecting adherence that were mirrored in SPIRES, highlighting the need to address these prior to allocating funds for other complex intervention rehabilitation trials.

The thesis has indicated that a future definitive trial is not feasible in its current design, however, potential solutions have been identified to address a range of challenges and areas of future research that could improve clinical practice in this under-represented patient group.

Appendix 1 Search strategy

Example from one database search.

Limiters for all searches: English Language

Updated search date: 26th and 27th April 2018

MEDLINE

Search ID #	Search Formula	Results
S1	orthostatic adj2 hypotension AB	641
S2	hypotension, orthostatic/ MeSH, AB	843
S3	postural adj2 hypotension AB	88
S4	orthostasis AB	138
S5	dizziness/ MeSH AB	2367
S6	“low blood pressure” AB	322
S7	hypotension/ MeSH AB	5181
S8	vascular adj2 response AB	645
S9	“autonomic dysfunction” AB	1519
S10	“cerebral blood flow” or “cerebral bloodflow” AB	5119
S11	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S9 OR S10	16541
S12	Elder* OR “older people” OR “older person” OR aged/ OR ageing OR aging OR senior OR geriatric AB	485281

S13	S11 AND S12	2436
S14	"non-pharmacological treatment*" OR "nonpharmacological treatment*" OR "non pharmacological treatment*" AB	455
S15	"non-pharmacological management" OR "nonpharmacological management" OR "non pharmacological management" AB	79
S16	"non-pharmacological intervention*" OR "nonpharmacological intervention*" OR "non pharmacological intervention*" AB	547
S17	14 OR 15 OR 16	1081
S18	Physical AB	218418
S19	S13 AND S18	396
S20	S11 AND S12 AND S17	9
S21	S11 AND S17	19
S22	compression ajd2 garment* AB	90
S23	compression adj2 stocking* AB	411
S24	compression adj2 bandag* AB	386
S25	compression adj2 wrap* AB	8
S26	stockings, compression/ AB	321
S27	abdominal binder AB	13

S28	S22 OR S23 OR S24 OR S25 OR S26 OR S27	1229
S29	S13 AND S28	11
S30	S11 AND S28	23
S31	S13 AND S17	8
S32	rehabilitation AB	954
S33	S13 AND S32	0
S34	S11 AND S32	1
S35	exercise AB	12723
S36	S35 AND S11	56
S37	S11 AND “physical maneuvers” or “physical manoeuvres” or “physical man*” or “physical measures” AB	25
S38	diet and S11	0
S39	fluid AND S11	0
S40	water AND S11	0
S41	meals AND S11	0
S41	food AND S11	0
S43	vasovagal AND management OR treatment AB	0
S44	S11 AND “head up” OR “head-up” AB	16
S45	S11 and “electrical stimulation” AB	2

S47	Parkinson* OR Alzheimer* OR dementia OR “multiple sclerosis” OR “motor neuron*” OR stroke AB	188454
S47	exp stroke/ MeSH AB	25475
S48	exp neurodegenerative disease*/ MeSH AB	52263
S49	exp dementia/ MeSH AB	24907
S50	exp multiple sclerosis/ MeSH AB	16962
S51	exp cerebrovascular disorder/ MeSH AB	47426
S52	exp brain ischemia/ MeSH AB	19725
S53	exp spinal cord injuries/ MeSH AB	19147
S54	exp brain injuries/ MeSH AB	15167
S55	craniocerebral trauma/ MeSH AB	2014
S56	exp central nervous system disease/ MeSH AB	197427
S57	exp brain damage, chronic/ MeSH AB	22074
S58	Parkinson* adj2 disease AB	20277
S59	S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58	197363
S60	S11 AND S59	2689
S61	S11 AND S17 AND S59	8

S62	S11 AND “functional electrical stimulation” OR FES OR “electrical stimulation” OR “neuromuscular stimulation”	0

AB: Abstract; KW: keyword; MeSH: medical search heading

Appendix 2 Excluded studies

Quasi-experimental studies

Chao CY and Cheing GL. The effects of lower extremity FES on the orthostatic responses of people with tetraplegia. Archives of Physical Medicine and Rehabilitation. 2005; 86(7):427-33.

Reason for exclusion based on inclusion criteria: Included a participant aged 15 years of age, therefore, did not meet eligibility criteria which was missed during full-text assessment. Inclusion criteria is ≥18 years. Unable to identify this participant in data presented.

Hilz MJ, Ehmann EC, Pauli E, Baltadzhieva R, Koehn J, Moeller S, DeFina P, Axelrod FB. Combined counter-maneuvers accelerate recovery from orthostatic hypotension in familial dysautonomia. Acta Neurologica Scandinavica. 2012; 126(3):162-70.

Reason for exclusion based on inclusion criteria: Included participant aged 15 years of age, therefore, did not meet eligibility criteria which was missed during full-text assessment. Inclusion criteria is ≥18 years. Unable to identify this participant in data presented.

Hohler AD, Amariei DE, Katz DI, DePiero TJ, Allen VB, Boyle S, et al. (2012) Treating orthostatic hypotension in patients with Parkinson's Disease and atypical Parkinsonism improves function. Journal of Parkinson's Disease. 2012; 2(3):235-240.

Reasons for exclusion based on methodological quality: Too many variables (reducing antihypertensive medications, maintaining hydration with 1500cc/day, decreasing dietary salt, wearing high compression stockings, and keeping the

head of bed elevated at 30 degrees when supine) This study has been excluded due to combined treatments and it is not possible to understand the effect of a given intervention.

Huang CT, Kuhlemeier KV, Ratanaubol U, McEachran AB, DeVivo MJ, Fine PR. Cardiopulmonary response in spinal cord injury patients: effect of pneumatic compressive devices. Archives of Physical Medicine and Rehabilitation. 1983; 64(3):101-6.

Reason for exclusion based on inclusion criteria: Included one participant aged 17 years of age, therefore, did not meet eligibility criteria which was missed during full-text assessment. Inclusion criteria is ≥18 years. Unable to identify this participant in data presented.

Sasaki K, Kaneyuki M, Fujii M, Ota A, Ota T and Nishigaki M (2013) Blood Pressure Dynamics During Long Sitting Position In Acute Ischemic Stroke Patients: Prevalence Of Orthostatic Hypotension. International Stroke Conference Poster Abstract.

Reason for exclusion based on inclusion criteria: Not an intervention. Testing for prevalence.

Sampson EE, Burnham RS and Andrews BJ. Functional electrical stimulation effect on orthostatic hypotension after spinal cord injury (2000). Archives of Physical Medicine and Rehabilitation. 139-143.

Reason for exclusion based on inclusion criteria: One of the six participants was aged 17 years of age. Inclusion criteria is ≥18 years. Unable to identify this participant in data presented. Did not meet eligibility criteria which was missed during full-text assessment.

Case report

Mikula J, Smith Pl, Meuleman, J and Levy CE. (201) Effects of a recreation therapy aquatics intervention: a case study of an older adult with uncontrolled orthostatic hypotension. American Journal of Recreation Therapy. American Journal of Recreation Therapy. 2010; 9(3):13-6.

Reason for exclusion based on inclusion criteria: Did not measure BP; HR not consistently measured, and no measurements reported. Did not meet eligibility criteria which was missed during full-text assessment.

Taylor PN, Tromans AM, Harris KR and Swain ID. (2002) Electrical stimulation of abdominal muscles for control of BP and augmentation of cough in a C3/4 level tetraplegic. Spinal Cord. 2002; 40(1):34-6.

Reason for exclusion based on inclusion criteria: No orthostatic tests therefore did not meet eligibility criteria which was missed during full text-assessment.

Appendix 3 Summary of findings table

Resistance exercise compared to no resistance exercise for older people and people with a neurological condition to treat orthostatic hypotension

Bibliography:

Brilla LR, Stephens AB, Knutzen KM, Caine D. Effect of strength training on orthostatic hypotension in older adults. Journal of Cardiopulmonary Rehabilitation. 1998; 18: 295-300.

Kanegusuku H, Silva-Batista C, Peçanha T, Nieuwboer A, Silva ND, Cost LA. et al. Effects of progressive resistance training on cardiovascular autonomic regulation in patients with Parkinson's disease: A randomized controlled trial. Archives of Physical Medicine and Rehabilitation. 2017; 98: 2134-2141.

Zion AS, De Meersman R, Diamond BE, Bloomfield DM. A home-based resistance-training program using elastic bands for elderly patients with orthostatic hypotension. Clinical Autonomic Research. 2003; 13: 286-292.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no resistance exercise	Risk difference with resistance exercise
Change in systolic blood pressure from supine to one-minute standing or 60 degrees head up tilt (sBP change) Assessed with: mmHg Scale from: 96 to 102.3 Follow up: range 8 to 12 weeks	148 (2 observational studies 1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	-	-	**SMD 0.04 SD higher** (0.31 lower to 0.4 higher)

Electrical stimulation compared to no electrical stimulation for older people and people with a neurological condition to treat orthostatic hypotension

Bibliography:

Yoshida T, Masani K, Sayenko DG, Miyatani M, Fisher JA, Popovic MR. Cardiovascular response of individuals with Spinal Cord Injury to functional electrical stimulation and passive stepping. Topics in Spinal Cord Injury Rehabilitation. 2013; 19: 40-41.

Kuznetsov AN, Rybalko NV, Daminov VD, Luft AR. Early poststroke rehabilitation using a robotic tilt-table stepper and functional electrical stimulation. Stroke Research and Treatment. 2013: 1-9.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no electrical stimulation	Risk difference with electrical stimulation
Change in mean arterial blood pressure when moving from supine to one-minute standing or a vertical position on a tilt table (MAP change) Assessed with: mmHg Scale from: 94.2901 to 110.5333333	268 (2 observational studies)	⨁◯◯◯ VERY LOW [d,e,f]	-	-	**SMD 0.24 SD lower** (0.54 lower to 0.07 higher)

Compression bandaging compared to no compression bandaging for older people and people with a neurological condition to treat orthostatic hypotension

Bibliography:

Gorelik O, Almoznino-Sarafian D, Litvinov V, Alon I, Shteinshnaider M, Dota E. Seating-induced postural hypotension is common in older patients with decompensated heart failure and may be prevented by lower limb compression bandaging. Gerontology. 2009; 55: 138-144.

Gorelik O, Shteinshnaider M, Tzur I, Feldman L, Cohen N, Almoznino-Sarafian D. Factors associated with prevention of postural hypotension by leg compression bandaging. Blood Pressure. 2014; 23: 248-254.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no compression bandaging	Risk difference with compression bandaging
Change in mean arterial blood pressure from supine to one-minute in sitting (MAP change) Assessed with: mmHg Scale from: 92.8 to 102.0666667	252 (2 observational studies)	⨁◯◯◯ VERY LOW [g,h,i]	-	-	SMD **0.16 SD lower** (0.41 lower to 0.09 higher)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **SMD:** Standardized mean difference; SD: Standard deviation; MAP: Mean arterial pressure; sBP: systolic blood pressure

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a) Before and after study, non-blinded, or blinding of investigators not reported; b). Variation in intervention: supervised sessions in Brilla; training performed four days per week in Zion, and three days per week in Brilla, twice a week in Kanegusuku; c) Small sample size in Zion, one third of which were withdrawn during the intervention phase; d). Observational study. No allocation concealment in Kuznetsov, participants randomised on day of admission; e) Heterogeneity in population, (e.g. stroke or spinal cord injury) and length of intervention (up to 30 days in Kuznetsov versus all testing on one-day Yoshida); f) Yoshida made conclusions based on muscle strength and cerebral blood flow, they did not make any conclusions about effect of intervention on orthostatic reactions, yet this was one of their objectives; g) Observational study (residual confounding, evidence); h) Before and after study, long-term effects not investigated. Study investigated seating induced orthostatic hypotension and did not measure effects in standing; i) Lead author and multiple co-authors were the same in both papers.

Appendix 4 Characteristics of included studies

Eight non-pharmacological interventions for OH were identified under two general categories: *physical modalities* (exercise, electrical stimulation, compression, compression and physical counter-maneuvers, physical counter-maneuvers, sleeping with head up) and *dietary measures* (food and fluid intake).

Physical Modalities

Exercise

Study	Country and Setting	Participant characteristics	Experimental Intervention	Control Intervention	Outcomes measured	Description of main results
Luther et al. 2008. Randomised crossover pilot trial using sequential testing	Germany, Neuro Rehabilitation Unit	N=9 unconscious within first three months of brain injury; (5 male) Mean age 51 (± 20) years	Tilt table with an integrated stepping device Intervention and control delivered in a random order on different days, one week between testing.	Conventional tilt table	**Primary**: interruption of verticalization due to a syncope or pre-syncope symptoms such as tachypnoea, tachycardia, pallor or increase in sweating. **Secondary**: state of consciousness according to Coma Recovery Scale-Revised (CRS-R); influence of treatment on muscle tone using	There were significantly more incidences of pre syncope on the conventional tilt table ($p<0.05$) at tilts of 50 or 70 degrees compared to the tilt table with integrated stepping. The binominal test as a cross-check showed significantly more treatment discontinuations on the conventional tilt table than on the tilt table with integrated stepping ($p=0.031$).

					Modified Ashworth Scale.	
Takahagi et al. 2014 Randomised controlled trial	Brazil, Outpatient	N=21 recurrent neuro cardiogenic syncope with had positive head up tilt test (three male) Mean age: 32 (±10) years in intervention group; 26 (±8) years in control group	N=11 undertook aerobic physical training using cycle ergometer for 12 weeks. Two supervised sessions plus two unsupervised sessions.	N=10 undertook 15 minutes of stretching and 15 minutes of light walking for 12 weeks. two supervised sessions.	Resting and training HR, VO2 peak, VO2 anaerobic threshold, sBP and dBP before and after 12-week training.	The Training Group exhibited a tendency for higher peak HR, with VO2 peak and VO2 anaerobic threshold than the control group. The training group exhibited a statistically significant difference($p<0.01$) in syncope episodes between pre- and post-intervention. There was a significant difference ($p<0.05$) in the number of negative Head up tilt (72.7% in the training group versus 30% in the control group).

Taveggia G RI. 2015. Randomised controlled trial	Italy, Neuro Rehabilitation Unit	N=12 with vegetative state or minimally conscious state 3-18 months after acute acquired brain injury (eight male) Mean age: 65 (±8) years in intervention group; 63 (±16) in control group	N=6 tilted to 65 degrees with a robotic tilt table system performing 18 steps per minute of the lower limbs (hip and knee flexion) for 30 minutes three times a week for 24 sessions.	N=6 tilted to 65 degrees for 30 minutes with no lower-limb movement.	HR and BP monitored at every tilt angle Coma recovery scale and level of consciousness scale pre- and post treatment; OH occurrence and length.	n=4 withdrawn due to medical events. Intervention group showed a progressive reduction in OH during treatment; n=3 showed a complete absence of OH at the end of rehabilitation therapy. Control group showed more serious OH after 24 sessions of treatment. BP readings not reported, but the group tilted with robotic stepping experienced less OH during verticalization (48 and 4 seconds) compared to the control group (120 and 187 seconds).
Rocca et al. 2016 Randomised controlled trial	Switzerland, inpatient hospital	N=30 (n=14 sub-arachnoid haemorrhage; n=4 severe brain trauma; n=4 intra-parenchymal haemorrhage, n=2 ischemic stroke, n=3 brain anoxia, n=3 other (17 male) Age range: 18-88 years	N=10 passive cycling in supine (Protocol Two) N=10 passive stepping with robotic tilt table (Protocol Three)	N=10 standard physiotherapy (Protocol One)	sBP and dBP, HR, respiratory rate, cerebral blood flow for participants with sub-arachnoid haemorrhage, venous blood and blood plasma samples.	No significant absolute or relative difference in any of the BP components with passive cycling or passive stepping.

		Mean age: 54.2 years				

Study	Country and Setting	Participant characteristics	Groups	Outcomes measured	Main description of results
Brilla LR SA. 1998. Quasi-experimental	USA, Community	N=24 elderly with orthostatic hypotension (a subset of n=53 participants from a larger study on a high-resistance strength training in older adults' study; all 24 showed orthostatic hypotension in the pre-test) (7 male) Mean age: 71 (±-5.8) years	All participants underwent eight weeks heavy resistance, progressive strength training program upper and lower limb. Participants were discontinued from the study if more than two consecutive sessions were missed.	1) Resting BP in supine, sitting and standing positions 2) Resting HR in supine, sitting and standing positions 3) Response to orthostatism in rising from supine after 10 minutes and rising from a chair after five minutes	Significant changes ($p<0.05$) in supine dBP (+3.2mmHg), sitting systolic BP (-3.9), and standing HR (+4.9 beats / minute). In response to orthostatic challenge, significant ($p < 0.05$) improvements in sBP (+9.7mmHg), dBP (+4.7) and HR (+3.2 beats/min) for the rise from chair, and in dBP (+6.7mmHg) rise from cot. Gains in strength were also noted.
Zion et al. 2003. Quasi-experimental	USA, Autonomic Function Laboratory at the Irving Centre of Clinical Research, Columbia University	N=12 orthostatic hypotension. Only eight completed the protocol. N=8 (four male) Age range: 63–81 years	N=8 completed an eight-week home-based resistance-training (HBRT) program using elastic resistance bands. Ten exercises (incorporating upper and lower limbs) were assigned and	Orthostatic testing: ECG and beat-to-beat BP continuously monitored and recorded. BP in supine, seated, standing one minute, standing two minutes, and during tilt table testing weeks one and eight at rest, 60 degrees tilt, end tilt.	At eight weeks, significant increases occurred in dynamic strength in the chest press ($p<0.017$), quadriceps extension ($p<0.017$), and leg press ($p<0.025$); no significant differences occurred in isometric strength or in BPs. Functional mobility increased in seven out of eight participants.

			customized to each participant.	Muscle strength testing (isometric and dynamic) Functional test of gait and mobility (Timed Up and Go) at baseline and eight weeks	No falls during the investigation period.

Study	Country and Setting	Participant characteristics	Experimental Group	Control Group	Outcomes measured	Main description of results
Kanegusuku et al. 2017 Randomised controlled trial	Brazil, Parkinson Association	N=30 Parkinson's Disease and n=16 healthy controls (33 male) Age range: 67 +/- 8; (Parkinson's Disease Training Group) Age range: 63+/- 8 (Parkinson's Disease Control Group) Age range: 68+/- 10 (healthy controls)	Parkinson's disease progressive resistance training (PDT)	Parkinson's disease control group (PDC) Healthy controls (HC)	sBP, HR, R-R intervals (Valsalva manoeuvre and orthostatic stress), muscle strength using one repetition maximum.	Compared with baseline, sBP fall was significantly reduced in the PDT group (14 ±11mmHg versus -6 ±10mmHg; PDC: -12 ±10mmHg versus 11 ±10mmHg; interaction P<0.05) In addition, after 12 weeks, these parameters in the PDT group achieved values similar to those in the HC group.)

Study	Country and Setting	Participant characteristics	Group A description and sample	Group B description and sample	Exposures/variables measured	Description of main results
Galizia et al. 2013. Case control study	Italy, Rehabilitation Hospital	N=42 elderly (Subset of n=90 diagnosed with orthostatic hypotension and proceeded to “active phase”) (four male) Mean age: 76.8 (±7.9) years	N=21 performed 10 full extensions of the ankle, knee, and hip joints of both limbs against a resistance band (6kg load) held under their feet whilst supine in bed	N=21 underwent testing, but did not perform any exercise prior to testing BP and HR	sBP and dBP after 10 minutes supine rest, immediately upon standing up, and after one, three- and five-minutes standing, HR, self-report orthostatic symptoms. Pre- and post-intervention. Medications taken at time of testing and intervention were recorded.	The reduction of sBP was significantly smaller ($p<0.01$) at each time interval after standing up in the exercise group than in the control group (10mmHg in the exercises group versus 27mmHg in the control group), but no difference observed in dBP or HR. Trend towards fewer OH symptoms in the exercise group compared to control during active testing (not significant).

Study	Country and Setting	Participant characteristics	Groups	Outcomes measured	Main description of results
Lopes P FS. 1984. Quasi-experimental	USA, Inpatient in Veterans Administration Medical Centre	N=12 SCI (12 male) Experimental group: n=5 with quadriplegia; n=1 with paraplegia, mean time	N=6 experimental group performed upper limb exercises whilst undergoing orthostatic training (tilted from 0 to 70 degrees at 10 degree increments at five-minute intervals on a tilt table)	BP and HR at 30 secs, 1.5, 2.5, three, four and five-minute intervals during tilt training. Each participant received a score 1-10 depending on step level at which they experienced orthostatic hypotension (at which time	Pre-test termination angle score homogenous between experimental and control groups ($p<0.1$). Mean differences in the termination angle Active, reciprocal, bilateral extremity exercise does not result in a significant

		since injury 7.2 weeks Mean age 40.3 years Control group: n=6 with quadriplegia, mean time since injury 8.2 weeks Mean age: 22.5 years	N=6 control group underwent orthostatic training (tilted from 0 to 70 degrees at 10 degree increments at five-minute intervals on a tilt table)	the test was terminated). Credit was given for partial completion of time specified at each angle by awarding 0.2 of a score for each 30-seconds completed.	change in tolerance of progressively higher vertical angles of tilt. The experimental group did not show increases in BP, nor demonstrate improved orthostatic tilt tolerance over the control group. Control group mean BP was 122/70mmHg and experimental group was 117/76mmHg

Electrical stimulation

Study	Country and Setting	Participant characteristics	Groups	Outcomes measured	Main description of results
Faghri and Yount 2002. Randomised controlled trial Repeated measures	USA, Rehabilitation Hospital	N=14 SCI (n=7 paraplegic n=7 tetraplegic, n=4 incomplete, n=10 complete) (11 male) n=15 healthy able bodied (gender not reported) Mean age SCI: 35 (±9.41) years	Fourteen SCI participants used a standing system: stationary standing for 30 minutes and dynamic standing using Functional Electrical Stimulation (FES) for 30 minutes. Four electrodes, balanced symmetrical biphasic waveform with 35 Hz frequency, duty cycles	Stroke Volume, cardiac output, HR, sBP, dBP, TPR, mean arterial pressure: measured in sitting, standing, after five minutes and 30 minutes of	Significant reduction in sBP and dBP ($p<0.05$) and mean arterial pressure during stationary standing in SCI subjects, whilst maintained in able-bodied. All of BP values were maintained to pre-standing levels in SCI during

		Mean age able bodied: 29 (±6) years	of 11 seconds on, 60 seconds off for channel one (tibialis anterior and gastrocnemius muscles) and seven seconds on and 64 seconds off for channel two (quadriceps and hamstrings muscle groups). Fifteen able-bodied participants performed stationary standing for 30 minutes and voluntary tiptoe contractions during 30 minutes of standing.	standing in all participants for both static and dynamic standing.	standing with FES. No changes in any variables for able-bodied participants. SCI participants demonstrated significant reductions ($p<0.05$) in all hemodynamic values for stationary standing at five and 30 minutes (able bodied-reduction in stroke volume and cardiac output at 30 min); compared to no change at five minutes when standing with FES, but at 30 minutes standing with FES there was significant increase in hemodynamic values (HR and stroke volume)- able-bodied maintained at five minutes, but at 30 minutes dynamic standing cardiac output decreased and HR increased.

Study	Country and Setting	Participant characteristics	Groups	Outcomes measured	Main description of results
Faghri et al. 2001 Quasi-experimental Repeated measures	USA, Rehabilitation Hospital	N=14 SCI (n=7 paraplegic n=7 tetraplegic, n=4 incomplete, n=10 complete) (11 male) n=15 healthy able bodied (gender not reported) Mean age SCI: 35 (±9.41) years Mean age able bodied: 29 (±6) years	SCI participants used a standing system for stationary standing for 30 minutes and dynamic standing using Functional Electrical Stimulation (FES) for 30 minutes (Active Standing Group). Four electrodes, balanced symmetrical biphasic waveform with 35 Hz frequency, duty cycles of 11 seconds on, 60 seconds off for channel one (tibialis anterior and gastrocnemius muscles) and seven seconds on and 64 seconds off for channel two (quadriceps and hamstrings muscle groups).Able-bodied participants performed stationary standing for 30 minutes and voluntary tiptoe contractions during 30 minutes of standing (Passive Standing Group).	Central hemodynamic responses of stroke volume, cardiac output, HR, mean arterial BP, total peripheral resistance, and rate pressure product during supine, sitting and standing positions, and every five minutes during the 30 minutes standing.	Overall, the tetraplegic group had a significantly lower sBP ($p=0.013$) and mean arterial pressure ($p=0.048$) than the paraplegics during passive standing. These differences were not detected during active standing. Moving from sitting to standing sBP increased 1.6% in the active standing group compared to a decrease in sBP of 8% in the passive standing group. When data were pooled from both groups and the overall groups response to active and passive standing were compared, the results showed that cardiac output, stroke volume, and BP significantly decreased ($p<0.05$) during 30 minutes of passive standing, whereas TPR significantly increased ($p<.05$). All hemodynamic variables were maintained during 30 minutes of active standing, and there were increases in RPP and HR after 30 minutes of active standing.

			With *versus* without order was counterbalanced.		
Elokda AS ND and SR. 2000 Quasi-experimental	USA, Rehabilitation Hospital	N=5 SCI, 2-4 weeks post-injury (n=2 tetraplegic and n=3 paraplegic) (all male) Age range: 26-36 years	All participants underwent repeated measures: supine on tilt table with feet in contact with footboard. Six minutes rest at 0 degrees for baseline measurements, followed by six four-minute stages for each tilt angle (0, 15, 30, 45 and 60 degrees), followed by a four-minute recovery. Repeated with and without electrical stim (Biphasic waveform, 20 Hz frequency without any ramping, alternating two seconds on and four seconds off periods of the quadriceps and ankle plantar flexors during the tilting procedure) Test terminated if SBP<60 or DBP<40 or severe orthostatic symptoms reported (fainting/headache).	sBP, dBP and HR taken at one-minute intervals during resting and tilting procedures (tilt angles: 0, 15, 30, 45 and 60 degrees). Subjective perception of orthostatic tolerance measured at one-minute intervals during tilting.	sBP showed a progressive decrease with increasing tilt angle without the electrical stim. The electrical stimulation treatment appeared to attenuate the rate of sBP decrease. sBP at each degree of tilt with Functional Neuromuscular Stimulation was higher. dBP was lower for all tilt angles without Functional Neuromuscular Stimulation.
Hamzaid et al. 2015.	Malaysia, Rehabilitation	N=2 sub-acute SCI (C7), 2	Both participants underwent four weeks of	sBP and dBP pre- and post-testing,	Subject A improved his orthostatic symptoms but did

Quasi-experimental	ward in medical centre and at one subject's residence after discharge	weeks since injury (both male) Age: 62 and 65 years	electrical stimulation (ES) therapy, four times per week for one hour per day. ES was applied on the rectus abdominis, quadriceps, hamstrings and gastrocnemius with 35 Hz frequency, pulse width 250 μs. The current amplitude was increased incrementally from 0 mA to the maximum tolerated by patients which was 130 mA.	every minute 0 to 65 degrees on tilt table, mean arterial pressure (MAP) and HR were obtained during pre-test and post-tests with and without ES-evoked muscle contractions. Symptom Scale Questionnaire for Orthostatic Intolerance was conducted during all tests to measure their OH symptoms.	not recover from clinically defined OH based on the 20-minute duration requirement. With concurrent ES therapy, 60 degrees head up tilt BP was 89/62mmHg compared with baseline BP of 115/71mmHg. Subject B fully recovered from OH demonstrated by BP of 105/71mmHg during the 60degrees head up tilt compared with baseline BP of 124/77mmHg. Both patients demonstrated longer tolerance time during head up tilt with concomitant ES (subject A: pre-test four minutes, post-test without ES six minutes, post-test with ES 12 minutes; subject B: pre-test four minutes, post-test without ES 28 minutes, post-test with ES 60 minutes).
Kuznetsov et al. 2013. Quasi experimental	Russia, Inpatient Stroke Rehabilitation Unit	N=128 mild or moderate stroke 4.6 ± 1.2 days post-stroke (56 male) Mean age: 58.3 (±1.2) years	N=38 were treated with ROBO-FES (robotic tilt table and functional electrical stimulation) for 30 days. A six channel stimulator was used and electrodes placed over biceps femoris, quadriceps femoris and gastrocnemius of either leg. Stimulation was synchronized with	British Medical Research Council Strength Scale; sBP and dBP; SV; cerebral blood flow using transcranial doppler ultrasonography, Barthel Index, Pulsatility Index, Resistance Index.	None of the participants in the ROBO and ROBO-FES groups had OH or orthostatic reactions when put into a vertical position, but 52% of the control participants showed OH. Does not state whether participants were doing any standing/vertical activities in the usual therapy as part of their rehabilitation.

			robotic leg movements varying between five and 100 mA. N=35 were treated with ROBO (robotic tilt table only) N=31 were the control group N=24 dropped out.	All measures taken at baseline and post-intervention	
Yoshida et al. 2013. Quasi-experimental	Canada, Outpatient Rehabilitation Centre	N=10 SCI, n=4 cervical spine; n=5 thoracic spine injury; 1-29 years since injury (6 male) Age range: 27-59 years	N=10 underwent the same testing and acted as their own controls. Tilted head-up to 70 degrees from supine; four 10-minute conditions involved, with a 10-minute rest between each condition: 1) passive head-up tilt with no intervention, 2) passive stepping using a motorized stepper (described in intervention section) 3) isometric Functional Electrical Stimulation (FES) of leg muscles (described in intervention section), and 4) dynamic FES of leg muscles combined with passive stepping (described in intervention section).	Participant report of any symptoms of orthostatic hypotension, such as headache, dizziness, and light-headedness. Inferior vena cava imaging in the transverse plane. EMG signals of the leg muscles were recorded only during STEP because cyclic passive movements of the legs can induce rhythmical EMG activities. Beat-to-beat BP recorded non-invasively every minute for 10 minutes during each of the testing conditions.	sBP decreased significantly during HUT and increased significantly during DFES, especially toward the end. dBP increased significantly during STEP and DFES. Mean BP increased significantly only during DFES. Statistical significance data for individual conditions not provided. However, results of a three-way ANOVA demonstrate that sBP, mean BP and HR all increased significantly (p=0.004, p=0.006 and p=0.026) during FES. Passive stepping significantly increased sBP, dBP and mean BP (p=0.009, p=0.182, p=0.0102). The effects of FES on SV and mean BP were greater than those of passive stepping. When combined, FES and passive stepping did not interfere with each other, but

			FES was applied to four muscle groups: tibialis anterior, hamstring, quadriceps femoris and triceps surae of both legs. Stimulation was bipolar and biphasic, with a maximum pulse width of 300 μs and stimulation frequency of 40Hz.		did not synergistically increase stroke volume or mean BP. Thus, the present study suggests that FES delivered to lower limbs can be used in individuals with SCI to help them withstand orthostatic stress.
Phillips et al. 2018 Quasi-experimental	Canada, Laboratory	N=5 SCI; n=4 cervical, n=1 thoracic), 3 years post-injury, (three male), all with OH. Age range: 23-32 years	All participants underwent the same testing, attending two testing sessions separated by at least one day. Once OH occurred, transcutaneous stimulation was applied to the skin between thoracic 7-8 spinous processes. The stimulation was delivered at 30Hz as monophasic, 1-ms pulses, to provide afferent input to the region of the spinal cord where sympathetic preganglionic neuron cell bodies are located. The current was increased from 10mA	Following 10 minutes of rest in supine, the test began with 15 minutes of supine measurements, after which participants were passively moved to the sit-up position and supported while sBP and dBP and HR measurements were recorded for an additional 15 minutes. Participants ranked their symptoms of nausea/ dizziness one to 10 (10 being most severe) each minute of the test	During the orthostatic challenge, all individuals experienced hypotension characterized by a 37–4mm Hg decrease in sBP, a 52–10% reduction in cardiac contractility, and a 23–6% reduction in cerebral blood flow (all $p<0.05$), along with severe self-reported symptoms. Electrical stimulation completely normalized BP, cardiac contractility, cerebral blood flow, and abrogated all symptoms. Non-invasive transcutaneous electrical spinal cord stimulation may be a viable therapy for restoring autonomic cardiovascular control after SCI.

			until BP normalized, up to a maximum 70mA, and maintained for at least one minute. Electromyography of the lower-limb skeletal muscles was recorded to confirm skeletal muscle contractions were not occurring and therefore the pressor responses were not attributed to the skeletal muscle pump of the venous vasculature.		

Compression

Study	Country and Setting	Participant characteristics	Experimental Intervention	Control Intervention	Outcomes measured	Description of main results
Podoleanu C MR. 2006. Single-blind randomised controlled trial Participants were blinded to treatment. Computer (blocked per	Italy, Hospital Clinic	N=21 elderly with symptomatic progressive OH (nine male) Mean age: 70 (± 11) years	All 21 underwent same testing conditions. Elastic compression bandage applied over the legs (40-60mmHg at the ankles and 30-40mmHg at the hips) for 10 mins, then an abdominal bandage was added for a	During active sham treatment, the same elastic bandages were applied (5mmHg overall).	Specific Symptom Scale Questionnaire for Orthostatic Intolerance (SSS-OI) (baseline and one-month post-treatment with elastic leg compression stockings. sBP and HR: supine and 60 degrees, pre- and post-leg bandage	In the intervention group, 90% of all participants remained asymptomatic versus 53% in the control group ($p<0.02$). During the month before evaluation, the mean SSS-OI score was 35.2 (± 12.1) with dizziness, weakness and palpitations accounting for 64% of the total score. The SSS-OI score

centre) randomised sequential order of treatments.			further 10 minutes (20-30mmHg). The modified Italian tilt protocol was used, consisting of 60 degrees passive tilting for 20 minutes followed by 0.4mg nitro-glycerine challenge for a further 20 minutes when the passive phase failed to induce syncope. Participants were trained and wore compression stockings (40-60mHg at ankles and 30-40mmHg at hips) for one month after testing.		phase, end of leg plus abdomen phase	decreased to 22.5 (±11.3) after one month of therapy ($p<0.01$). In the control group, sBP decreased from 125 (±18) mmHg immediately after tilting to 112 (±25) mmHg after 10 minutes of sham leg bandaged and to 106 (± 25) mmHg after 20 minutes despite the addition of sham abdominal bandage. In comparison, active therapy group BP was 129 (±19) mmHg, 127 ±17mmHg ($p<0.003$vs control), and 127 (±21) mmHg ($p<0.002$ vs. control).
Vijayakumar et al. 2012. Randomised controlled trial	India, Department of Rehabilitation Medicine	N=26 acute/sub-acute stroke (duration < 4 weeks post-stroke) with OH (18 male)	N=13 received Pneumatic abdominal binder (PAB) 40mmHg pressure and Pneumatic Calf Compression	N=13 received Elastic Compression Bandaging (ECB) from the metatarsal head to the popliteal	Number of days taken to attain orthostatic stability Modified Rankin scale (mRS) to measure	The percentage of participants <4 weeks post-stroke wearing pneumatic abdominal binder and pneumatic calf compression achieving orthostatic

		Mean age: 59.77 (±17.03) years in intervention group and 63.33 (±15.83) in control group	(PCC) 30mmHg pressure	fossa in a single layer spiral manner with overlap	independence of specific tasks. Hemodynamic responses, measuring sBP and dBP, and HR parameters at 0, 30, 45 and 60 degrees tilt.	stability was significant on the third (50%) (p<0.019) and sixth day (100%) (p<0.007). No significant difference in the mRS scores between groups.
Fanciulli et al. 2016. Single-blind crossover RCT	Austria, Laboratory and community	N=15 with Parkinson's Disease and orthostatic hypotension; (eight male) Age range: 66-75 years	After three days of testing, all participants received an elastic abdominal binder (20 ±2 mm Hg pressure). Binder worn for two hours and then assessed (pre- and post). After a one-day interval abdominal binder (20 ± 2mmHg) worn daily (daytime) for four weeks.	All participants underwent baseline tilt-testing, wore an abdominal binder (20 ±2 mm Hg pressure) or placebo binder (3 ±2 mm Hg pressure applied on the abdominal wall) for two hours, re-tested on the tilt table and subsequently removed the binder. After one-day washout, the tests were repeated to ensure all participants had	**Primary**: mean BP changes at three, five and 10 minutes in supine, 60 degrees verticalization and active standing. **Secondary**: Orthostatic Hypotension Questionnaire (OHQ), Orthostatic Hypotension Symptom Assessment (OHSA) and Orthostatic Hypotension Daily Activity Scale (OHDAS) scores after four-week open-label period.	Compared to the placebo binder, the abdominal binder was associated with an increase of the third minute tilt mean BP by 10 (±10.2 mmHg; +3.5, +14.5 (p<0.006). During the open-label phase, 12 patients wore the abdominal binder an average of 5.6 ±0.6 days/week, 50% to 75% of daytime. At 4-week follow-up, the OHQ score decreased by -2.2 points (p<0.003), the OH Symptom Assessment (OHSA) sub score by -1.7 points (p< 0.003) and the OHDAS by -3.9 (p< 0.007). No side effects occurred

				been tested in both abdominal and placebo binder. Participants then wore an abdominal binder (20 ± 2mmHg pressure applied on the abdominal wall) every day during the daytime for four weeks		during the crossover phase.
Wadsworth B. Randomised crossover trial	Australia, Large university-affiliated referral hospital	N=14, SCI T5 or above Age range: 18-73 years	Abdominal binder fitted to provided firm support around the abdomen from the anterior superior iliac crest to the costal margin of the rib cage (no mmHg pressure provided) Participants wore the abdominal binder daily for the duration of the trial (6 months)	Participants acted as their own controls and underwent testing in both conditions	Mean arterial BP Respiratory measures (peak expiratory flow, forced expiratory flow, forced vital capacity) Voice measures Measured at three time points: six weeks, three and six months, in supine and sitting in own wheelchair.	There was no statistically significant improvement in mean arterial pressure, maximal expiratory pressure or sound pressure level. Overall, an abdominal binder resulted in a statistically significant improvement in forced vital capacity ($p<0.005$), forced expiratory volume in one second ($p<0.05$), peak expiratory flow ($p<0.02$), maximal inspiratory pressure

			N=3 participants ceased wearing the binder daily. No data provided on daily wearing time.			(p<0.01), and maximum sustained vowel time (p<0.01).
Figueroa JJ SW. 2015. Randomised crossover trial	USA, Laboratory	N=13 with neurogenic orthostatic hypotension, (n=5 PAF; n=4 multiple system atrophy; n=2 Parkinson's disease; n=1 post-radiation baroreflex failure; n=1 autoimmune autonomic neuropathy. (seven male) Age range: 62-79 years Participants were ambulatory and able to stand for at least 3 minutes without developing pre-syncope.	Abdominal and physical maneuvers All participants performed four maneuvers: moving from supine to standing without abdominal compression; moving from supine to standing with either a conventional or adjustable abdominal binder, application of subject-determined maximum pressure tolerable while standing; and whilst still erect, subsequent	All participants moved from supine to standing without abdominal compression, then with either a conventional or adjustable abdominal binder. The adjustable binder involved the application of participant determined maximum pressure tolerable while standing. Participants were asked to stand up and adjust the compression to a maximal tolerable level, and then	**Primary**: Continuous sBP, dBP and HR in supine, and standing **Secondary**: The Orthostatic Symptom Scale (OSS) (Visual Analogue Scale); The Symptom Change Scale (SCS) (Visual Analogue Scale)	Standing without abdominal compression resulted in a large orthostatic fall (ΔsBP, -57mmHg) and severe orthostatic intolerance (OSS, five points). Compared with no abdominal binding, 10mmHg of abdominal compression while supine prior to rising was effective in attenuating OH with both the conventional (ΔsBP, −50mmHg; IQR, −33 to −70mmHg; p=<0.03) and pull string (ΔsBP, −46mmHg; IQR, −34 to −75mmHg; p<0.01) binders.

			reduction of compression to a level the subject believed to be tolerable for a prolonged period.	subsequently reduce the compression to a level the subject believed to be tolerable for a prolonged period. It was unclear if this was immediate or within a specific time of standing.		
Gorelik et al. 2004. Randomised crossover trial	Israel, Hospital inpatient	N=61 admitted with acute medical conditions requiring bed rest (n=11 acute coronary syndrome; n=10 pulmonary oedema; n=14 cerebrovascular accident; n=21 infectious diseases; other n=5) (41 male) Mean age: 77.8 (±9.7) years	All participants underwent testing with or without compression bandages applied to both legs from ankle to thigh before moving from supine to seating. Extensible bandages were used obtain a uniform pressure of about 30 mmHg. The bandages were stretched along both legs so that the designed		BP, ECG tracing, HR, O2 saturation, dizziness and palpitations were recorded prior to seating and during one, three, and five minutes in sitting.	Prevalence of postural hypotension was identical in the unbandaged versus bandaged state (55.7%). However, dizziness, palpitations, accelerated HR and decreased oxygen saturation over five minutes were more prevalent in the unbandaged versus bandaged state ($p<0.01$, $p<0.001$, $p<0.05$, $p<0.001$, respectively). In the unbandaged state, presence versus absence of OH was

			rectangles were transformed into squares.			associated with significantly greater incidence of palpitations, tachycardia and decline of oxygen saturation over time (p< 0.04, p<0.03, p<0.03, respectively.

Study	Country and Setting	Participant characteristics	Groups	Outcomes measured	Main description of results
Gorelik et al. 2009.	Israel, Inpatient Medical Department	N=108 acute decompensated heart failure (n=53 postural hypotension, n=27 dizziness and/or palpitations, n=10 cardiac arrhythmias) (48 male) Mean age: 75.1 (± 8.3) years	Compression extensible bandages were applied along both legs from the ankle to the thigh before seating. The bandages were stretched so that the designed rectangles were transformed into squares to obtain a uniform pressure (40 mm Hg at the ankle). All participants underwent the same testing: Two sessions. Day one bandages but without compression; Day two compression bandages of approximately 40mmHg pressure.	BP, HR, Oxygen saturation, and the occurrence of dizziness or palpitations were recorded prior to, and during one, three and five minutes in sitting.	Compression bandages prevented postural hypotension in 21 of 49 patients and decreased the degree of postural BP fall (p<0.001). sBP and dBP were higher in the bandaged group (sBP 146.6±31.1mmHg bandaged versus 141±28.1mmHg unbandaged p=0.055; dBP 72±13.9 bandaged versus 68.7±16.9 unbandaged p=0.05) following one minute of sitting, and 147±28.6mmHg bandaged versus 141±27.1 p=0.03 sBP; 72.4±14.6 bandaged versus 67.9±17.4 unbandaged p=0.01 for dBP following five minutes of sitting.

			Participants assisted from supine to sitting - not standing		
Gorelik et al. 2014.	Israel, Hospital inpatient	N=73 bedridden for ≥8 hours with diagnosed OH with various acute medical conditions (22 male) Mean age: 75.2 (±9.0) years	Before moving from supine into sitting, compression extensible bandages were stretched along both legs from the ankle to the end of the thigh, so that the designed rectangles became transformed into squares, to obtain a uniform pressure of about 30–40 mmHg at the ankle. All participants underwent same testing: day one no compression, day two compression.	sBP and dBP, Heart Rhythm with ECG, self-report symptoms of OH in supine and at one, three and five minutes of sitting.	Compared with the non-bandaged state, OH was registered in only 53.4% of bandaged participants ($p<0.001$). Moreover, the appearance of orthostatic hypotension symptoms decreased to 34.2% ($p<0.001$). On the second day (bandaged), supine dBP values were higher in the persisting 82.1±18mmHg versus non-persisting OH group 73.6±14mmHg ($p<0.027$). In the bandaged state, OH symptoms were significantly reduced in the non-persisting OH group 35.3% ($p<0.003$). In participants with persistent OH, sBP was significantly increased wearing bandages (147.0±28mmHg) versus unbandaged (136.2±26.5) ($p<0.004$)
Henry et al. 1999. Quasi-experimental	United Kingdom, Outpatient Falls Clinic	N=10 elderly with OH (six male) Age range: 62-89 years (mean 77.2 years)	All participants underwent same testing: supine rest then positioned into standing 90 degrees upright with tilt table	sBP and dBP, HR in supine; one, two and three minutes in supine and 90 degrees tilt.	Short-term efficacy with compression hosiery in elderly people with symptomatic OH and a history of falls. (Not reported if OH was reason for falling or other factors)

			for three minutes, then positioned into supine. Elastic compression hosiery (tights) fitted to bilateral lower limbs	Authors refer to the fact that orthostatic dizziness was abolished in seven out of 10 participants, but do not report how this was measured.	
Denq JC O-GT. 1997. Quasi-experimental	USA, setting not reported	N=14 confirmed diagnosis of OH (n=3 Multiple System Atrophy; n=9 PAF; n=2 diabetic autonomic neuropathy) (five male) Age range: 31-78 years	All participants underwent testing from supine to 80 degrees head-up tilt ± compression (40mmHg) to calves/thighs/abdomen and all compartments combined to evaluate the impact compression of different body parts on orthostatic BP and tolerance.	Visual Analogue Scale (numerical) rating change in symptoms and duration of stand with compression garments; sBP and dBP in supine and 80 degrees verticalization, HR, end diastolic volume index, CO, index peripheral resistance index. Visual Analogue Scale of severity of symptoms after each session.	Head-up tilt with compression resulted in significant improvement ($p<0.001$) of sBP 115.9±7.4mmHg compared to 89.6±7.0mmHg without compression. Maximum improvement was with all combinations of compression. Abdominal compression alone was the only single compartment to significantly reduce OH ($p<0.01$). Participants reported that a combination of all compartments was most efficacious in reducing symptoms.
Lucas and Ainslie, 2012 Quasi-experimental	New Zealand, Laboratory	N=12 healthy older and younger adults N=6 older adults (six male) Mean age: 70 (±4) years N=6 younger adults (six male)	All 12 participants stood up rapidly (<5 secs) and remained free standing for three minutes, then returned to supine for six minutes and repeated the supine-to-stand protocol. Standing was terminated and	Oesophageal temperature, skin temperature, blood flow velocity, arterial BP (beat-to-beat changes in BP), cardiac output from HR and SV, TPR in supine and standing.	All participants completed the normothermic and passive heat conditions of both control and compression leggings. No difference in supine or initial seconds in standing in either groups. In minute six of standing those wearing compression leggings in the normothermia increased total

		Mean age: 29 (±4) years	participants positioned supine with legs elevated if pre-syncope symptoms presented. This was completed at normal body temperature and repeated at elevated body temperature (0.5 degrees Celsius). In the elevated temperature trials participants wore long-sleeved and legged, two-pieced, tube-lined perfusion suit. Passive heating was achieved by circulating warm water through the suit and wrapping participants in reflective foil blanket with periodic warm water circulation to maintain the elevated temperature.		peripheral resistance in older participants but dropped in younger participants. In contrast, standing and heated, wearing compression leggings lowered total peripheral resistance in older and younger adults.
Rimaud D CP. 2012. Quasi-experimental	France, Department of Physical Medicine and Rehabilitation	N=9 SCI (n=4 above T6, n=5 below T6), at least 2 years post injury (nine male) Age range: 25-54 years	All participants performed two maximal wheelchair exercise tests using a wheelchair ergometer (increasing Watts every two minutes) without and with	VO2/ VCO2 measurement during test, sBP, dBP, finger arterial pressure, SV, Q, Total peripheral resistance, HR variability, wavelet	No differences in VO2, W max, HR or BP with or without GCS. Significantly higher ($p<0.05$) LF wavelet and lower HF Wavelet (HF wavelet is a parasympathetic marker) with GCS 3-8 minutes post exercise. Decrease in mean

			Garment Compression Stockings (GCS) (21mmHg (ankle) to 15 mmHg (calf). The progressive wheelchair test started with a 30-minute rest period using the wheelchair ergometer to stabilize various cardiorespiratory variables. This was followed by a six-minute warm up at a constant speed with no load. The load was then increased by 10W increments for low-level paraplegics and 5W for high-level paraplegics, every two minutes until volitional exhaustion, or the subjects were unable to maintain the required speed.	high and low and very low frequency power. All tested pre- and post-exercise sitting in wheelchair, without GCS and with GCS. Norepinephrine and epinephrine	relative risk with GCS immediately after exercise. Norepinephrine at rest was significantly higher ($p<0.05$) with GCS. Epinephrine and norepinephrine both increased with exercise with and without GCS.
Helmi M LA. 2013. Case Report	Netherlands, Intensive Care Unit	N=1 post-operative cervical C3/C4 laminectomy tetraplegic with clinically significant compromise of	Tilt table testing from supine 0 to 45 degrees and 60 degrees and back to supine) without, and then with inflatable external leg compression (ELC) to	sBP and dBP in 0, 45 and 60 degrees tilt, SVI, HR, PI, peripheral perfusion tissue oxygenation.	With the application of 15 mmHg pressure during 45 and 60 degrees head up, SVI and HR were maintained, and no presyncope symptoms occurred. With the ELC constantly inflated with a pressure of 15

		cardiovascular control, (male) Age: 61 years	bilateral lower limbs (calf and thigh)		mmHg, the participant could remain in the upright position and could be mobilized during physiotherapy wearing inflatable ELC. ELC succeeded in improving presyncope symptoms and preventing OH for several hours.

Physical counter maneuvers

Study	Country and Setting	Participant characteristics	Groups	Outcomes measured	Main description of results
Ten Harkel et al. 1994. Randomised crossover trial	Netherlands, Academic Medical Centre	N=13 (n=7 orthostatic hypotension (n=4 PAF, n=1 Hodgkin's disease, n=1 medulla oblongata bleed, n=1 multiple sympathectomies); n=6 healthy controls) (11 male) Age range: 20-65 years	Intervention group: leg muscle pumping (tiptoeing) or tensing (leg crossing) for one minute, started after two minutes of active standing. Maneuvers were performed in a random order, each for one minute, with one minute of quiet standing in between. Control group: active standing	sBP and dBP, HR; SV, CO, peripheral resistance assessed before standing (10 seconds) and after one minute of tiptoe, quiet standing and leg crossing assessed over 10 seconds at first and after one and two minutes in standing.	Mean BP, sBP and dBP significantly decreased in patient group ($p<0.01$) following one minute of standing; SVR did not change from supine; rise in HR seen mainly in patients due to non-PAF patients. Tiptoeing did not result in a clear distinction between initial and sustained effects between PAF and non-PAF patients. Leg-crossing induced an initial increase in BP, SV and CO both in normal participants and patients with PAF and non-PAF. There was a small increase in mean arterial pressure of only 13mmHg in the patient group, but the authors suggested that this increase is of a similar magnitude to the changes seen in pharmacological interventions such as

					fludrocortisone, erythropoietin and midodrine.
Bouvette CM MB. 1996.	USA, Laboratory and community	N=9 with neurogenic OH (n=5 PAF; n=3 autonomic neuropathy; n=1 multiple system atrophy) (4 male) Mean age: 53 (± 18) years	N=9 underwent four training sessions in the laboratory, then performed the physical counter-maneuvers at home for 3-4 months Physical counter-maneuvers: Squatting; genuflection-contraction; leg crossing; knee flexion; toe raise; neck flexion; abdominal contraction; thigh contraction. Session one: all physical counter-maneuvers performed in random order; Sessions two and three: biofeedback training on three maneuvers selected by the participant that provided the best symptomatic relief to optimize performance;	Global Symptomatic Improvement Score (GSIS) judging the effectiveness of physical counter-maneuvers; improvement in orthostatic BP and continued improvement with follow-up telephone survey. BP measured at baseline, before and after each counter-manoeuvre.	GSIS: The findings support the hypothesis that physical counter-maneuvers can significantly increase BP. Squatting produced the most dramatic change in arterial pressure (40.6 +23.2mmHg) ($p<0.0004$). Continued improvement: Standing time improved by 8.33 ±5.8mmHg minutes. Participants reported continued counter-manoeuvre performance of 3.83 ±3.1mmHg maneuvers per day. Biofeedback training: Statistically significant improvement seen with genuflection-contraction ($p<0.002$), leg crossing ($p<0.016$) and thigh contraction ($p<0.007$) after three or four 45 minutes sessions.

			Session four: practicing maneuvers without feedback.		
van Lieshout et al. 1992.	Netherlands, Outpatient	N=13 (n=7 hypo-adrenergic OH; n=6 healthy) OH (four male); age range 18-65 years N=6 healthy controls (gender not reported); age range: 28-34 years	All participants performed exercises in fixed order: Stand up; cross legs; squat. Stand for 10 minutes max or until symptoms. Then cross legs for 30 seconds then resume standing. Squat when "BP became low again" (BP cut off not described)	sBP and dBP measured in all three positions.	Standing without any physical maneuvers, five out of seven participants reported orthostatic dizziness within 10 minutes (four unable to remain standing). After leg-crossing all participants could stand for 10 minutes or more with a difference of 14mmHg (SD±6) in mean BP. A larger increase in sBP was observed with squatting with a difference of 44 (SD±18).
Smit AA HM. 1997.	Netherlands, Laboratory	N=8 OH (n=5 autonomic failure, n=2 post-acute panautonomic neuropathy, n=1 post-extensive sympathectomy) (three male) Age range: 35-70 years	Each participant sat on seats of varying heights (48cm, 38cm, 20cm) and performed different maneuvers such as squatting, crossing legs and standing in a crossed-leg position.	sBP and dBP, HR, CO, SV and TPR. All measures taken: *Standing*: with and without contraction of crossed legs; *Sitting*: with and without leg-crossing sat on Derby chair, Fishing chair and footstool; *Squatting*.	BP was higher in sitting than standing. Due to increase in SV and CO. Lower chairs associated with high increment in BP. Crossing legs on the Derby chair produced greater increment in sBP and dBP ($p<0.01$) (mean change 16mmHg and 9mmHg no leg crossing and 49mmHg and 25mmHg with leg crossing). Standing crossing legs increased sBP and dBP significantly ($p<0.01$) (14mmHg and 7mmHg standing and no leg crossing versus 29mmHg and 15mmHg crossing legs in standing) and in seven out of eight of the participants, produced a higher increase than sitting on the derby chair. Sitting on a fishing chair

					was perceived as most comfortable. Derby chair was deemed unstable / did not relieve symptoms/ small seat. Low stool was hard to stand up from; uncomfortable or experienced dizziness on standing.
Tutaj M MH. 2006. Quasi-experimental	Not reported (author has been contacted)	N=17 familial dysautonomia (nine male) Mean age: 26.4 (±12.4) years	Physical counter-maneuvers: bending forward, squatting, leg crossing, and abdominal compression using an inflatable belt. Counter-maneuvers were initiated after standing up, when sBP had fallen by 40mmHg or dBP by 30mmHg, or presyncope had occurred.	HR, sBP and dBP, mean BP, CO, TPR and calf volume	Mean BP increased significantly ($p<0.005$) during bending forward 20.0mmHg, squatting ($p<0.002$) 50.8mmHg and abdominal compression 5.8mmHg ($p<0.04$) but not during leg-crossing. Squatting and abdominal compression also induced a significant increase in cardiac output during squatting ($p<0.02$) 18.1mmHg and during abdominal compression 7.6mmHg ($p<0.014$).

Physical counter-maneuvers and compression

Study	Country and Setting	Participant characteristics	Groups	Outcomes measured	Main description of results
Smit AA WW. 2004.	Netherlands, Laboratory	N=23 neurogenic orthostatic hypotension (n=4 PAF, n=7 multiple system atrophy, n=8 progressive autonomic neuropathy, n=3 subacute panautonomic neuropathy, n=1 OH post extensive sympathectomies) (10 male) Age range: 35-79 years	All participants performed Protocol one: evaluated in a 40–60 degrees head up-tilt position, the effect of abdominal compression on caval vein and femoral diameter, arterial BP and haemodynamics wearing an anti-gravity suit. Protocol two: anti-gravity suit standing, then standing and legs crossed with 20mmHg abdominal compression, 40mmHg abdominal compression All participants performed Protocol three: investigated the ability to maintain standing BP by an elastic binder (nine or 12 inch),	sBP and dBP in supine, 40 degrees head-up-tilt, 15 seconds preceding compression, first 15 seconds of 40mmHg lower abdominal compression, last 15 seconds of 40mmHg compression and 5 seconds after compression and in standing with graded pressure 20/40mmHg ± leg crossing. HR, CO, TPR, and changes in the inferior caval and femoral vein diameter.	Protocol one (n=7) HUT from supine. Compression resulted in an increase in BP with increase in SV and CO and no change in peripheral resistance diameter of veins, decreases caval vein but femoral vein increases. Protocol two (n=12) binding and countermeasures increased BP but there was no significant difference between conditions. Protocol three n=9 significant increase in BP ($p<0.05$) (11mmHg sBP and 6mmHg dBP) and increase SV (13% $p<0.05$) and CO (12% $P<0.05$) and reduction in peripheral resistance -7% $P<0.05$) Elastic abdominal compression increased standing BP with 15/6mmHg (range -3/3 to 36/14, $p<0.05$).

			compression 15-20mmHg		

Sleeping with head-up

Study	Country and Setting	Participant characteristics	Groups	Outcomes measured	Main description of results
Ten Harkel et al. 1992. Quasi-experimental	Netherlands, Academic Centre (Two patients were tested on an out-patient basis, while the other four were admitted to hospital)	N=6 hypo adrenergic OH (three male) Age range: 23-65 years	Each patient received a diet containing 150-200mmol sodium and a minimal water intake of 2000 ml per day. This three-week study was divided into one-week phases. To assess changes during the steady state alone, the first three days of each week were excluded from the analysis; values are presented as the average for the last four days of each period. Interventions were delivered in one-week blocks. In the first week (control) they did not have medication (apart from two bedridden patients	Orthostatic tolerance as measured by Orthostatic Disability Score; maximum standing time, terminated either at the onset of severe orthostatic dizziness or after a maximum period of 10-minute standing; sBP, dBP and mean BP) for control; head-up tilt; head-up tilt and fludrocortisone, and follow-up; Fluid balance (changes in total body water content assessed by measuring changes in body weight). Follow up at 14 months	Combined treatment reduced orthostatic dizziness in all patients ($p < 0.001$), and increased the maximal standing period to at least 10 min. HUT alone (n=4) reduced the BP decrease after 1 minute of standing from -64/-42/-25±27/21/17mmHg to -53/-37/-23±31/24/20mmHg ($p<0.01$ for sBP). The addition of fludrocortisone to HUT (HUT/fludro) (n=5) further reduced the BP decrease after one minute of standing from -63/-40/-24±20/12/11mmHg to -21/-19/-8±12/10/5 ($p<0.05$ for sBP, mean and dBP). BP at maximal standing time increased during combined treatment 58/47/42±9/8/7mmHg initially to 95/69/57±27/22/20mmHg ($p<0.05$ for sBP and mean BP), and remained unchanged during the

			because of severe OH who had 0.1 mg fludrocortisone) or head tilt. In the second week all patients started to sleep in the 12 degrees HUT position. During the third week treatment involved a combination of sleeping in the HUT position and fludrocortisone administered at 2200 hours.		14-month (range 8-70 month) follow-up period.
Fan et al. 2011 Randomised controlled trial	In participants' own homes. Country not reported	N=100 with OH Mean age 76 years	Intervention group n=66, control group n=34. Intervention group had the head of their bed elevated six inches with blocks for six weeks.	Hemodynamic variables: sBP, dBP (24-hour ambulatory blood pressure), MAP, HR, cardiac output, stroke volume, total peripheral resistance. Plus, weight, frequency of dizziness, 24-hour urinary sodium and volume, and presence of ankle oedema.	Sleeping with head up six inches for six weeks was tolerated by participants and both groups reported overall improvement and had fewer episodes of dizziness per week before versus after (p=0.0039). Participants sleeping with head up were more likely to have leg oedema. Compliance to the treatment was 77%. However, there were no significant differences between the two groups in hemodynamic variables. Changes in sBP between pre and post were: -1.45mmHg supine and 1.98 mmHg standing; dBP 2.42 mmHg

					supine and 2.61mmHg standing, MAP 0.94 mmHg sitting and 2.07 mmHg standing. Study concluded that sleeping head up six inches for six weeks is not recommended as an outpatient treatment for OH in elderly people.

Dietary measures

Food intake

Study	Country and Setting	Participant characteristics	Groups	Outcomes measured	Main description of results
Loew F GL. 1995.	Switzerland, Teaching Hospital	N=10 PD (n=2 diagnosed with OH) (five male) Mean age: 81.6 (± 9.02) years N=10 age matched hospital in-patient controls (3 male) Mean age: 85.3 (± 5.23) years	Testing over two consecutive days. Day one: BP monitoring every 30 minutes in supine between 0800 and 1800 hours. Supine sBP readings were used before the start of lunch and 60 minutes after a normal 2500kj lunch to measure the postprandial sBP change Day two: participants received their usual breakfast and pursued their usual activities in the ward (newspaper reading or rest). PD participants received their usual physio mid-morning and afternoon, orthostatic BP in active standing and head-up tilting tests performed after a	sBP, HR in supine, active standing and head-up tilt testing both pre- and post-prandial. dBP was recorded but not presented in the literature. Day one BP testing in supine, day two testing in sitting.	PD participants had a significant ($p<0.01$) postprandial sBP drop from 154.3±26.2 to 127.7±18.1mmHg in supine position compared to healthy controls; in PD participants the drop was moderately correlated to orthostatic sBP responses and significantly correlated to the pre-prandial supine baseline systolic BP. There was a greater fall of sBP with passive than with active standing with both groups, which was greater in the PD group. No difference in orthostatic HR responses between groups.

			normal 2500kj lunch (lunch eaten in sitting). All participants underwent orthostatic tests: active standing and head-up tilting tests, performed 60 and 40 minutes before the start of lunch.		
Mader SL. 1989.	USA, Clinical Research Centre	N=26 healthy elderly and young adults (16 male) N=10 healthy young Age range: 19-31 years N=16 healthy elderly Age range: 55 to 78 years.	All participants underwent the same testing: Three recumbent BPs measured two minutes apart after five minutes supine rest. The subject stood up and BP was measured one minute later. Protocol was performed beginning at 2.30pm on admission and 1pm the following day at discharge. Readings included first thing in the morning 7am, before and after meals, mid-morning, mid-afternoon, mid evening and bedtime	sBP and dBP, HR.	Supine BP: elderly had higher sBP and dBP. HR was higher in both groups after meals. Standing sBP and dBP was similar between groups. The younger group had higher HR with standing. Older showed drop pre- to post-meal BP (not seen in young). HR was higher post-meal in both groups. After overnight rest standing BP was the same.

			(1030pm). Postural BP protocol was performed 45 minutes after the beginning of each meal.		
Puvi-Rajasingham S and Mathias CJ. 1996.	United Kingdom, Inpatient	N=7 primary autonomic failure with severe OH (n=3 PAF with no other neurological deficit; n=4 Shy-Drager syndrome (Multiple System Atrophy) (four male) Age range: 45-69 years	All participants underwent same conditions: first day three meals, versus second day (at least one day apart) six meals. Total calorie intake was the same.	BP monitoring and self-initiated readings after five minutes of lying, sitting or standing. With only three meals participants have extra set of positional recordings (six in total same as a six-meal day). Participants kept a symptom diary.	Regardless of meal the size, drop in BP with positional change was similar but three meals showed a significantly lower BP in all positions than six meals (131mmHg after large meals and 151mmhg after small meals $p<0.005$). Between meals a larger drop in BP was seen with three meals (88mmHg versus 104mmHg sBP $p<0.002$ and 48mmHg versus 63mmHg $p<0.0001$ dBP). Fewer OH symptoms were experienced with six meals.

Fluid intake

Fluid intake AND exercise

Study	Country and Setting	Participant characteristics	Groups	Outcomes measured	Main description of results
Humm AM ML. 2008. Quasi-experimental	UK, Laboratory	N=8 PAF diagnosed with OH, all able to walk (three male) Mean age: 63.9 (±6.1) years	All participants underwent same testing: Supine 10 minutes rest, standing 10 mins, rest in supine, exercises in supine (pedal ergometer), rest in	sBP and dBP in supine one (rest), standing one (five minutes standing), supine two (rest), cycling (exercise), supine three (rest), stand two.	All participants had severe OH pre-exercise with prompt recovery of BP in supine. Five minutes after drinking water, there was a significant ($p<0.05$) rise in BP in supine position. With exercise there was a clear fall in BP (sBP 42.1 (SD±24.4) mmHg and dBP

			supine, standing five minutes. Identical protocol followed on two separate occasions: one of which participants drank 480ml distilled water at room temperature within five minutes after first stand. Participants were randomly assigned to start with the protocol without water (n=3) and with water (n=5) with on average 10.8 days between the two assessments. Participants were asked to drink the water within five minutes.	HR, subjective perception of hypotension related symptoms.	25.9 (SD±10.0) mmHg) with a modest risk in HR, this occurred even after water ingestion. sBP remained low after exercise but was significantly higher ($p<0.05$) after water intake two and five minutes of standing (74.5 (SD±32.9) mmHg and 74.3 (SD±28.4) mmHg without water versus 103.5 (SD±34.4) mmHg 89.0 (SD±16.7) mmHg with water), resulting in better tolerance of post-exercise standing.
Shannon et al. 2002. Quasi-experimental	Germany, Autonomic Dysfunction Centre	N=18 primary autonomic failure (n=9 PAF, n=9 multiple system atrophy) (12 male) Age range: 35-70 years Plus an additional n=9	Participants drank 120mls, 240mls, and 480mls of tap water at room temperature (20 degrees Celsius) in less than five minutes on separate days. All participants underwent Protocol one: drinking 480mL of tap water at room	Blood pressure (supine, seated, upright); HR Protocol one: Seated, BP and HR measured every five minutes for 30 minutes, standing, returned to seated for a further 35 minutes with BP and HR taken every five minutes,	Before water drinking, seated BP was 117± 23/67±10mmHg which fell to 83± 20/53±11mmHg after one minute of standing. Thirty-five minutes after drinking 480mls of water at room temperature in less than five minutes improved seated BP increased to 150± 25/78 ±13 mmHg and after standing for one-minute BP was 114± 30/66 ±18mmHg.

		females with idiopathic orthostatic intolerance Mean age: 36 (± 4) years	temperature (20 degrees C) in less than five minutes. All participants underwent Protocol two: consumption of standardized high carbohydrate breakfast.	standing BP determined. Protocol two: seated for 30 minutes and BP and HR taken every five minutes, participants ate a meal, then BP and HR taken every five minutes for 90 minutes whilst seated. Repeated twice (once with water before the meal, one meal only). Valsalva manoeuvre, hyperventilation, cold pressor, hand grip.	Pre-meal BP 138± 41/77 ±17 mmHg. Within 20 minutes after starting to eat, BP decreased, reaching a nadir of 43± 36/20 ±13mmHg below baseline after 90 minutes. Drinking 480mls of water in less than five minutes prior to a test meal, BP increased with a peak that was 36± 23/9 ±10mmHg above baseline after 20 minutes ($p<0.001$ ANOVA compared to meal with no water). Drinking water attenuated orthostatic tachycardia in patients with idiopathic orthostatic intolerance (123 ±23 beats per minute at baseline to 108 ±21 beats per minute after water drinking.) [Inconsistencies in reported number of participants between the methods and participant characteristics.]
Young and Mathias, 2004. Quasi-experimental	United Kingdom, Inpatient Neurological Hospital	N=14 chronic autonomic failure and severe OH (n=7 multiple system atrophy) (four male) Mean age: 62 (±9.5) years	All 14 participants underwent the same testing: Standing BP and HR were measured before and 15- and 35-minutes following ingestion of 480 ml distilled water within five minutes. Patients remained seated for 15 minutes	sBP and dBP before, and 15 and 35 minutes after ingestion of 480ml distilled water. Calculation of CO, TPR, and SV using Modelflow analysis.	Standing prior to water ingestion caused a significant fall in sBP in all patients (110.6 ±25.1mmHg seated and 79.5 ±21.5mmHg standing $p<0.01$). After water ingestion standing sBP was significantly higher ($p<0.001$) at 15 minutes (101.0 ±23.3mmHg) and 35 minutes (99.6 ±24.0mmHg), with an

		(n=7 PAF) (3 male) Mean age: 59 (±10) years	after water ingestion, with beat to beat cardiovascular indices measured with the Portapres II device with subsequent Modelflow analysis.		improvement in orthostatic symptoms. The time to first significant rise in seated BP occurred at five minutes post-water ingestion in PAF and at 13 minutes in MSA. These increases were accompanied by increases in total minutes post peripheral resistance, reaching significance by five minutes in PAF and 13 minutes in MSA. There were no significant changes in CO, SV, or ejection fraction.

Abbreviations: BP: blood pressure; sBP: systolic BP; dBP: diastolic BP; HR: heart rate; O2: oxygen; VO2: maximum rate of oxygen consumption; VCO2: maximum rate of expired carbon dioxide; OH: orthostatic hypotension; CO: cardiac output; SVR: systemic vascular resistance; SV: stroke volume; SVI: stroke volume index; PI: perfusion index; SCI: spinal cord injury; PD: Parkinson's disease PAF; pure autonomic failure; TPR: total peripheral resistance; ECG: electrocardiogram; R-R: intervals between successive heartbeats; RPP: rate pressure product; HUT: head up tilt; FES: functional electrical stimulation; DFES: dynamic FES; IFES: isometric FES; STEP: passive stepping; USA: United States of America; UK: United Kingdom

Appendix 5 Statistical analysis plan

SPIRES
STANDING PRACTICE IN REHABILITATION EARLY AFTER STROKE

RESEARCH WITH PLYMOUTH UNIVERSITY

Statistical Analysis Plan

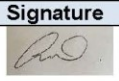
Standing Practice In Rehabilitation Early after Stroke (SPIRES)

A randomised controlled feasibility trial to investigate the effects of a functional standing frame programme versus usual physiotherapy to improve function and quality of life and reduce neuromuscular impairment in people with severe sub-acute stroke

Contents

1 Administrative Information

Title of Trial	Standing Practice In Rehabilitation Early after Stroke (SPIRES) A randomised controlled feasibility trial to investigate the effects of a functional standing frame programme versus usual physiotherapy in people with severe sub-acute stroke on function, quality of life and neuromuscular impairment
Trial registration number	ISRCTN15412695
IRAS number:	201646
REC Reference:	16/WA/0229
Funding Source:	National Institute for Health Research Clinical Doctoral Research Fellowship Award, ICA-CDRF- 2015-01-044
Protocol Version:	1.2 03/06/2017
SAP Version:	1.0 17/10/2018
SAP Revisions:	

	Name	Signature	Date
Statistical Analysis Plan Authored by:	Chief Investigator: Angie Logan Faculty of Health and Human Sciences School of Health Professions Peninsula Allied Health Centre Plymouth University Derriford Rd Plymouth PL6 8BH United Kingdom		24/10/2018
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2 Abbreviations

AE	Adverse Event
ADL	Activities of Daily Living
BI	Barthel Index Activities of Daily Living
EQ-5D-5L	European Quality of Life-5 Dimensions
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
PHQ-9	Patient Health Questionnaire-9
RCT	Randomised Controlled Trial
SPIRES	Standing Practice In Rehabilitation Early after Stroke
SADQ-10	Stroke Aphasia Depression Questionnaire-10
SAE	Serious Adverse Event
SAQOL-39	Stroke & Aphasia Quality of Life Scale-39
SAP	Statistical Analysis Plan
SRU	Stroke Rehabilitation Unit
TMG	Trial Management Group
TSC	Trial Steering Committee
VAS	Visual Analogue Scale

3 Introduction

Background and rationale for the trial

The full background and rationale for the trial can be found in the SPIRES study protocol (Logan *et al.*, 2018). In summary, SPIRES is a randomised controlled feasibility trial to determine whether a functional standing frame programme (a novel combination of prolonged standing and task-specific strength training of sit to stand) is feasible for people with severe stroke.

Purpose of statistical analysis plan

The trial protocol includes an outline of the statistical methods to be employed in the analysis of the trial data. The purpose of the Statistical Analysis Plan (SAP) is to provide full details of the planned statistical methods to be used in the primary report of the trial results. However, it is worth noting that, SPIRES is a feasibility trial, therefore formal statistical analysis and hypothesis testing is not appropriate and thus will not be undertaken.

Trial objectives and outcome measures

The aim of this feasibility trial is to obtain the necessary data and operational experience to determine the future planning of an intended definitive multi-centre RCT. The RCT compares a three-week functional standing frame programme with usual physiotherapy to determine effectiveness of improving function, quality of life and minimising secondary neuromuscular impairments in people who have had a severe stroke as part of their inpatient sub-acute rehabilitation. Potential primary and secondary outcome measures for a future definitive RCT are detailed in Section 7 (Analysis). The following trial outcomes, categorised into feasibility indicators for process, resource, management, and safety parameters (Table 1), will be measured during trial:

Process

Eligibility criteria: The suitability and feasibility of eligibility criteria will be determined by reviewing reasons for exclusion documented in the Approach/Screening Log and Screening and Post-Screening Case Report Forms and reviewing characteristics of recruited participants as documented in the Screening and Post-Screening Case Report Forms.

*Ability to consent**: The ability of patients to consent will be measured by percentage and calculated by dividing the number of patients who provided informed consent by the number of consultee declarations plus the number of participants who provided informed consent (multiplied by 100). Additionally, reported incidence of cognitive and communication impairments will be measured from the Screening and Post-Screening and Assessor Case Report Forms. [*Determined by mental capacity not doubted by physiotherapists based on cognitive and communication ability]

Consent rate: The consent rate will be measured by percentage and calculated by dividing the number of individuals who consented to participate in the trial, by the number who meet the inclusion criteria (multiplied by 100). This will provide a percentage of participants who consented from the number of admissions at each site and all SRUs combined. Reasons why eligible individuals were not interested in participating will be recorded by the PI/recruiting therapist in the approach/screening logs.

Recruitment rate: The recruitment rate will be measured by percentage calculated by dividing the number of participants recruited per month by the number of participants who

met the inclusion criteria (multiplied by 100). This information was recorded in the study log at each site.

Willingness/ability of physiotherapists to recruit: The willingness or ability of physiotherapists to recruit will be measured by percentage and calculated by subtracting the number of patients screened and approached from the number of eligible admissions and dividing by the number of participants screened documented on the Approach/Screening Log and multiplying by 100.

Willingness of participants to be randomised: The willingness of patients to be randomised will be measured by percentage and calculated by the percentage of patients who did not want to enrol in the trial (people who did not want to enrol divided by all eligible participants multiplied by 100, as documented on the Approach/Screening Logs.

Retention rate: The retention rate is an indication of acceptability and will be measured by percentage and calculated by dividing the number of participants who completed data collection at post-intervention, 15, 29 and 55 weeks follow-up by the number of participants who completed data collection at baseline, multiplied by 100.
NB: *The published protocol states follow-up visits will be undertaken at 3, 6 and 12-months post-randomisation. However, once follow-up assessments had commenced it was identified that these visits were 3, 6 and 12 months plus three weeks (to allow for the intervention period) post-randomisation.* However, the same conditions/time periods were applied to all participants.

Acceptability of the intervention: Acceptability of the intervention amongst participants, relatives and physiotherapists will be measured in four ways at three different time points (i.e. pre-, during and post-intervention): 1) recruitment rate; 2) percentage of withdrawals (the inverse of retention rate); 3) adherence; 4) qualitative data collected via semi-structured interviews with participants, their relatives and physiotherapists and a focus group with physiotherapists.

Determining usual physiotherapy: Usual physiotherapy management for people who have had a severe stroke receiving inpatient early sub-acute stroke rehabilitation will be captured by the Control Group Case Report Forms.

Sample size estimates: Data from this feasibility trial, in particular standard deviations of the potential outcome measures, together with existing literature, will help to inform power calculations for subsequent trials.

Primary outcome: Data from this feasibility trial will determine which primary outcome measure will be used for a subsequent main trial. This will be based on a number of criteria: acceptability of the outcome measures (to participants, relatives and physiotherapists), the completeness of the outcome measure, lack of floor/ceiling effects, likely ability to detect change, indicative sample size calculation and emerging evidence.

End point: Data from this feasibility trial will determine the primary end point of a subsequent main trial.

Resource
Burden: Burden is defined as "the perceived amount of effort that is required to participate in the intervention" (Sekhon, Cartwright & Francis, 2017 p.7) and will be measured for both participants and physiotherapists. Participant burden will be measured in four ways: .

Participant burden will be measured in four ways: 1) by percentage and calculated by dividing the number of patients who did not want to enrol in the trial (people who did not want to enrol divided by all eligible participants multiplied by 100) ; 2) physical and psychological effort using the brief interview assessment at the end of each intervention session; 3) semi-structured interviews; 4) withdrawals.

Physiotherapist burden will be measured in three ways: 1) willingness/ability to recruit (see above); 2) semi-structured interviews and focus group with physiotherapists; 3) field notes from Chief Investigator's blinded assessments.

Cost effectiveness: Estimates of resource use and related costs for the delivery of SPIRES will be measured through semi-structured interviews exploring time required for preparation for functional standing programme session.

Management

Participant adherence: Adherence of the functional standing frame programme will be measured by tracking 1) total number of sessions attended; 2) total number of minutes standing; 3) total number of sit to stand repetitions; 4) reasons for non-completion of sessions; 5) enjoyment; 6) effort; 7) fatigue; 8) aches and pains, as documented by treating physiotherapists in the Case Report Form (Table 2).

Acceptability of outcome measures: The feasibility of the proposed outcome measures will be measured by proportion of primary and secondary outcome measures completed, and ability to detect change in this patient group with severe mobility impairment.

Fidelity: Intervention fidelity, defined as adherent delivery of the intervention, will be evaluated using a trial-specific SPIRES checklist that outlined all components of the functional standing frame programme intervention, and usual physiotherapy control group to be completed by an independent observer (e.g., physiotherapist checked blood pressure, demonstrated, ensure foot sensors in situ and positioned safely, position participant in frame etc.).

Orthostatic Hypotension Protocol: In this trial, OH is assessed in sitting because participants with severe stroke are unable to move from lying into standing in one manoeuvre. It is anticipated that some participants may have OH in standing that did not have OH in sitting. We will assess the number of incomplete sessions for those diagnosed with OH either in sitting (as part of the assessment for minimisation process) or during the participants' initial stand. Additionally, the type (pharmacological or non-pharmacological) and rationale for OH interventions will be captured including the feasibility and acceptability of abdominal binder in people with contraindications, e.g. percutaneous endoscopic gastrostomy.

Safety

Safety will be assessed by comparing the number and nature of serious adverse events (SAEs) and adverse events (AEs) in the intervention group with those in the control group (Tables 3 and 4).

The AE risks of taking part in this trial have been assessed to be low (Logan *et al.*, 2017). Adverse events such as chest infections and urinary tract infections, which are common in people with stroke, will not be monitored and not required to be recorded for any participants. Treating physiotherapists will, however, be asked to record musculoskeletal aches and pains, falls (both before, during and after the physiotherapy sessions) and worsening neurological symptoms from the initial physiotherapy assessment.

Serious Adverse Events (classified below) will be recorded and each site will notify Peninsula Clinical Trials Unit. Peninsula Clinical Trials Unit will routinely notify the Chief Investigator (CI) by email of all reported SAEs as they occur and will report organ system listings of all SAEs to the TSC and Sponsor on a quarterly basis.

Serious adverse events are classified as:

- results in death
- is life threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect
- or is considered by the investigator to be an important medical event

All adverse and serious adverse events will be cross tabulated by treatment group and assessed for clinical relevance to inform the design and conduct of a full trial. The relatedness of AEs and SAEs to the intervention group will also be presented (Table 5).

Measures of adherence

In line with the objectives of this feasibility trial, it is important to understand adherence levels within the functional standing frame programme. As such, completion of the three-week intervention with a minimum of five and maximum of seven sessions per week will be reported (Table 2). In addition, physiotherapists are advised to implement 30 minutes of prolonged standing, 8-12 repetitions of sit to stand, and 15 minutes of usual physiotherapy for each session. In both cases (duration of standing and repetitions of sit to stand) adherence will be reported in the form of the total number and percentage of non-adherers.

4 Trial methods

Trial design

A pragmatic multi-centre feasibility randomised controlled trial with blinded assessment in patients who have had a severe stroke.

The recruitment target is fifty patients with confirmed diagnosis of new or recurrent stroke, classified as severe (using either the mRS or the NIHSS). Participants will be recruited from three healthcare sites (four Stroke Rehabilitation Units) in Cornwall and Devon. Participants will be randomised on a 1:1 basis to either the control group, where they received usual physiotherapy, or to the intervention group where they will receive the functional standing frame programme for three weeks during their inpatient stay in sub-acute Stroke Rehabilitation Units.

Participants will be assessed at baseline, post-intervention (3 weeks post-randomisation) (+/-1 week), and 15-, 29- and 55-weeks post-randomisation (+/- 1 week).

Randomisation and Allocation Concealment

Randomisation will be conducted by means of a central, secure, password-protected web-based system created and managed by Peninsula Clinical Trials Unit in

conjunction with the trial statistician. Randomisation will be performed using a minimisation algorithm to balance groups in terms of the minimisation variables (fatigue and orthostatic hypotension (OH)):

1. fatigue (4-10 Visual Analogue Scale score Vs. no/minimal fatigue (0-3 Visual Analogue Scale score)
2. OH (hypotension Vs. no hypotension)

Exact details of the setup of the minimisation algorithm will be confirmed between the trial statistician and the PenCTU programming team only. Minimisation characteristics in allocated groups is show in Table 6.

Blinding

Due to the nature of the intervention, it will not be possible to blind the trial participants or treating physiotherapists. However, assessors are blinded, and participants asked not to reveal their treatment allocation during assessments.

The success of blinding in this trial will be assessed by asking blinded assessors to guess the trial group assignment and comparing these responses to what would be expected by chance (Table 7).

Sample Size

One of the key purposes of a feasibility trial is to inform sample size calculations for a full-scale trial. As such, the mean, SD and range at each follow-up at 15, 29 and 55 weeks for each outcome measure will be calculated. Then, accounting for the uncertainty in these standard deviations as appropriate, well-informed sample size calculations can be obtained. Indicative sample sizes will be calculated conservatively for each of the primary outcomes. Furthermore, recruitment, retention and dropout rates will be calculated and presented to suitably account for this in the determination of the sample size for the full-scale trial. It is anticipated that in any future main trial, the primary outcome would be of a continuous nature and analysis of covariance (ANCOVA) would be used for the primary analysis.

Sample size calculation

As a feasibility trial, a formal sample size calculation based on considerations of power is not appropriate; this trial is not powered to detect between-group clinically meaningful differences in a primary outcome. One of the aims of this trial is to provide robust estimates of the likely rates of recruitment and follow-up, as well as provide estimates of the variability of the proposed primary and secondary outcomes to inform sample size calculations for the planned definitive trial. There is no consensus on the recommended number of participants required for a feasibility trial, with published "rules of thumb" ranging from 20 to 70 or more participants, when the planned primary outcome is of a continuous nature. A recent paper recommended a feasibility trial sample size should recruit 25 participants per allocated group, if the planned definitive trial will have a two-arm parallel group design, a continuous primary outcome and have 90% power and two-sided 5% significance level, to detect a "small" standardised effect size (Whitehead *et al.*, 2016). Therefore, this feasibility trial aims to recruit 50 participants in total.

Participants will be recruited from four different Stroke Rehabilitation Units (three healthcare sites), providing access to 67 beds. The planned recruitment period will be 52

weeks and over this period, across the three sites, it is anticipated that approximately 130 potential participants would be approached and estimated that around 50% of eligible participants would consent to participate.

Given the nature of the trial, with measures being collected at baseline, post-intervention (three weeks post-randomisation), and 15-, 29- and 55-weeks post-randomisation (± one week), with time required for travelling between sites and qualitative interviews, logistically it was estimated that the maximal recruitment rate is five to six participants per month.

A target sample size of 50 participants allowed the follow-up rate to be estimated to within ±15%. The follow-up rate is estimated to be 70%, which would provide follow-up outcome data on a minimum of 35 participants across both allocated groups and three sites.

Statistical interim analysis

There is no planned interim analysis for this trial. If, for any reason, the TSC requests an interim analysis of the data, the trial statistician will undertake such work, to retain the blinding of the Chief Investigator.

Criteria for progression to full trial

Progression to a full trial will be supported based on the following criteria:

	Criteria	Scenario 1	Scenario 2	Scenario 3
1	% of recruitment target achieved (50 participants)	≥70%	51-69%	≤50%
2	Target figure = 75% of the percentage of participants randomised to the intervention group who participated in at least three sessions per week of the functional standing frame programme. This includes an estimated dropout rate of 25% due to mortality (Brønnum-Hansen *et al.*, 2001; Fang *et al.*, 2012)	≥70% of the target figure	51-69% of the target figure	≤50% of the target figure
3	Target figure = 60% of the percentage of participants randomised who completed their 29- and 55-weeks post-randomisation follow-up assessment. This includes an estimated 40% drop out rate due to mortality (Brønnum-Hansen *et al.*, 2001; Fang *et al.*, 2012).	≥70% of the target figure	51-69% of the target figure	≤50% of the target figure
	Proposed action	Proceed to submitting plan to funder for full trial	Discuss with TSC and funder about progression and resources needed to achieve target	No progression to plan a full trial in the current design

If any one of these criteria meets scenario 3 the trial would not progress in its current design.

Timing of final analysis

Statistical analysis will be undertaken once the final group of participants have completed the final assessment at 55 weeks post-randomisation and the database is locked.

Timing of outcome assessments

All proposed outcome measures will be collected at baseline, post-intervention at 3 weeks post-randomisation (+/-1 week), and 15-, 29- and 55-weeks post-randomisation (+/- 1 week). The percentage of assessments completed within +/- 1 week will be recorded. If these targets are being missed, it may be necessary to consider widening this time frame to allow inclusion of data from more patients (Table 8).

5 Statistical Principles

Statistical Significance Levels

As a feasibility trial, there will be no hypothesis testing undertaken.

Adherence to treatment

Participants may not complete their allocated treatment because of medical issues such as fatigue, deterioration of health or further strokes, or participants may simply decide that they no longer want to continue with the intervention. The likelihood of this occurring could be increased due to the acute nature of the stroke as well as the severity and complexity of their impairments from their severe stroke. In this scenario, the number and proportions of participants categorised as non-adherers will be summarised for each group separately and overall, alongside the details of the deviation, but there will be no formal statistical testing undertaken. The analysis will be completed on an intention to treat basis.

Adherence to allocated treatment

The number of sessions completed and reasons for non-adherence will be recorded in both the control and intervention group. In addition, in the intervention group the number of minutes standing per week and the number of sit to stand repetitions completed each week will be recorded (Table 2).

This data will be presented by site according to stroke severity (moderately severe or very severe as classified by the modified Rankin Scale) to allow an assessment of adherence with stroke severity, and measure of association with adherence computed if appropriate to do so for the data in hand (Table 9). Data will also be explored graphically (Figure 1) to look at the relationship between adherence and three key factors: orthostatic hypotension, fatigue and proposed primary outcome measures. Existing literature does not provide any clear guidance of what the number of sessions or number of minutes to have an effect centrally or peripherally, therefore, understanding what the minimum amount for adherence is necessary

Analysis Populations

The principal analysis on the primary and secondary outcome measures (in the form of summary statistics, not formal analysis) will be undertaken on both an Intention To Treat (ITT) and Per Protocol (PP) basis. The feasibility of this intervention for people with severe stroke is unknown, and physical disability, fatigue, cognitive and communication impairments may affect their ability to adhere to the protocol. Therefore, both ITT and PP analysis is

recommended to enable readers to interpret the results (Schulz, Altman & Moher, 2010). An ITT analysis will analyse participants according to their random allocation, regardless of adherence to the protocol or lack of participation or completion if allocated to the intervention group. ITT is generally accepted to be the gold standard approach as it provides a conservative estimate of the intervention effect as it would likely be seen in practice. In addition, a PP analysis will provide an estimate where only those participants who strictly adhered to the protocol will be analysed. This will be defined as completion of a minimum of five sessions per week, 30 minutes of standing, 15 minutes of usual physiotherapy and eight sit to stand repetitions for the intervention group, and completion of a minimum of five sessions per week of 45 minutes of usual physiotherapy. The definition of per protocol analysis will be based on a definition of adherence determined following assessment of the data (see "Adherence" above).

In the case of a patient being randomised in error, with a later discovery that they were in fact ineligible, a decision will be made by the Trial Management Group as to whether they should be removed from the trial completely or retained on an ITT basis.

Data Sources and Data Quality

The data from this trial will come from information entered onto Case Report Forms (CRFs) completed by treating therapists (for the intervention and control groups during the three-week intervention period) and blinded assessors at baseline, post-intervention at 3 weeks (+/-1 week) post randomisation, and 15-, 29- and 55-weeks post-randomisation (+/- 1 week).

6 Trial population

Data from the screening process through to the completion of the trial will be recorded and presented following The Consolidated Standards of Reporting Trials (CONSORT) (Eldridge *et al.*, 2016) guidelines for pilot and feasibility trials (see Figure 1).

Inclusion and exclusion criteria

The trial population will be people who:

1) Have a new (first/recurrent) clinical diagnosis of stroke, cerebral haemorrhage or infarct confirmed by consultant or CT scan leading to admission to the Stroke Rehabilitation Unit
2) Are aged ≥18 years
3) Are graded as mRS 4 or 5 and/or NIHSS≥16 (severe or very severe stroke and unable to stand without support/mechanical aid and assistance of two people)
4) Are able to give informed consent or assent received from a consultee (see recruitment section)
5) Are conscious and responsive to verbal commands.

People meeting any of the following criteria will be excluded from participating in the trial:

1) Systolic blood pressure ≤100mmHg or ≥220mmHg at rest lying or sitting
2) Oxygen saturation ≤87% with or without supplementary oxygen (e.g. severe acute/chronic cardiorespiratory disease)

3) Resting heart rate of ≤40 or ≥110 beats per minute (e.g. cardiovascular instability)
4) Temperature ≥38.5 degrees centigrade or ≤35 degrees centigrade
5) Orthopaedic impairments which prevent full weight bearing in standing
6) Malnutrition Universal Screening Tool score of ≥2, or deemed to be not meeting nutritional demands for therapeutic interventions by dietician
7) Documented clinical decision for receiving end of life care
8) Unstable coronary or other medical condition that is judged by the PI/CI or clinical team to impose a medical risk to the patient by involvement in the trial
9) Assessed functionally by specialist clinicians as being a risk to themselves or others due to their inability to follow non-verbal prompts or are behaving erratically
10) Immobile and not weight bearing pre-stroke
11) Additional neurological deficits unrelated to the current or past stroke (e.g. peripheral neuropathy or Multiple Sclerosis), because these impairments are not related to the condition of interest)
12) Weight of 115kg or more, this is the weight limit on the standing frames
13) Being discharged out of county, e.g. admitted during holiday/visit to Cornwall or Devon because they would be unable to participate in follow-up assessments
14) If people are registered in another trial the CI will be contacted to ensure there is no contamination between trials
15) Non-English speaking.

Participants who discontinue, withdraw or are lost to follow-up

It is possible that participants will withdraw consent part way through the trial, or their treatment may be discontinued due to medical reasons. Participants who withdraw or discontinue will be categorised into one of the following:

- Continue to consent for follow-up and data collection
- Consent to use pre-collected data only
- No further follow-up of data collection

Reasons for withdrawal or loss to follow up will be summarised in the CONSORT diagram where possible, at each stage of the process (withdrawal prior to randomisation, patients who did not receive their allocated treatment, non-completion of treatment, lost to follow-up).

Participants who withdraw from the trial, or whose treatment is discontinued on medical grounds, will not be replaced although their available data will be used unless they have

specifically requested for it to be removed from the database. The extent of discontinuation, withdrawal and loss to follow up will be used to inform the design of the fully powered subsequent trial, predominantly to ensure a sufficiently powered trial after drop-out.

Baseline characteristics and demographics

Baseline characteristics, collected prior to randomisation, will be cross-tabulated according to allocated treatment group to informally check for balance between groups and provide an exploratory overview of the data (Table 10). Collected baseline data will include:

- demographic information including gender, age, weight, marital status, place of residence, living arrangements, employment status and pre-admission level of mobility
- Medical and surgical conditions including previous strokes
- Mobility status at time of consent (equipment and whether assistance is required)
- Diagnostic data including severity of stroke, classification of stroke/lesion location
- Days since stroke admitted to Stroke Rehabilitation Unit and commencing the intervention or control group
- Prevalence of aphasia, orthostatic hypotension and fatigue.

7 Analysis

Completeness of proposed outcome measures

A key measure of interest is the completeness of the data, for both proposed primary and secondary outcomes. The total number of missing data and corresponding proportions will be presented for each outcome at each time point. In addition, for the potential primary outcomes, a breakdown of data completeness by individual measure/aspect will be presented where possible (Table 11).

Definitions of proposed outcomes

Outcomes are presented in the order in which they will be summarised and collected at five time points: baseline, post 3-week intervention, 15 weeks post-randomisation, 29 weeks post-randomisation and 55 weeks post-randomisation.

Proposed primary outcome measures

The primary outcome measures proposed for the main trial are function-based (Table 12). The Barthel Index (BI) (Mahoney & Barthel, 1965) is frequently used in stroke clinical trials, although was not designed specifically for clinical trials or the stroke population. The BI rates a person's degree of independence performing functional selfcare (feeding, grooming, bathing etc.) and mobility activities (transferring in/out of bed/chair, walking etc.). A major limitation of the BI is its floor effect (Quinn, Langhorne & Stott, 2011) and as a result has limited ability to detect change at extremes of ability, making it less discriminating in severe stroke (Schepers *et al.*, 2006).

This feasibility trial provides the opportunity to investigate whether an alternative functional outcome measure is more sensitive and responsive to change in people with severe stroke and can be used in both inpatient and community settings for both the acute and chronic stages of stroke. Therefore, the Edmans Activities of Daily Living Index for Stroke Patients (Edmans & Webster, 1997) will also be used. This measure

covers all the categories included in the BI, however, the degree of independence is more detailed than dependent/independent for each item assessed. It was developed specifically for people with stroke, both as an inpatient in the sub-acute phase as well as in the community setting in the chronic phase. Collecting both these outcomes will enable investigation of the clinical utility and responsiveness of two functional outcome measures, which will help determine which measure is most appropriate for any follow-on main trial.

Both the BI and the Edmans Activities of Daily Living Index for Stroke Patients will be self-report. However, given the prevalence of communication and cognitive impairments, participants may be unable to report this information or may have reduced insight into their actual versus perceived abilities. In such cases, where it is not possible to obtain all the outcome measurement data from the participant, the researcher will obtain by proxy data from the treating physiotherapist during inpatient admission or next of kin/carer, once discharged from hospital. The proportions completed by the participants and proxy will be summarised (Table 12).

Proposed secondary outcome measures

The secondary outcome measures proposed for the main trial will capture the multiple aspects of secondary neuromuscular, physiological and psychological complications observed post-stroke that may impede functional recovery and can change rapidly within the first two to three months' post-stroke (Table 14).

Knee muscle strength using hand held dynamometer (Hyun *et al.*, 2015; Riddle *et al.*, 1989)

Length of hip flexors, hamstrings and ankle plantar flexors using manual universal goniometer (Berryman & Brandy, 2010)[9]

Muscle tone in hip adductors, hamstrings and ankle using Modified Ashworth Scale (Ghotbi *et al.*, 2009)

Control of trunk using Trunk Control Test (Duarte *et al.*, 2009; Verheyden *et al.*, 2006)

Mood using Patient Health Questionnaire (PHQ-9) (Williams *et al.*, 2005) for participants who have nil or mild to moderate aphasia, or Stroke Aphasia Depression Questionnaire-10 (SADQ-10) for participants who have severe aphasia (Sutcliffe & Lincoln, 1998)

Health related quality of life using Stroke and Aphasia Quality of Life Scale-39 (Hilari *et al.*, 2003) and the EQ-5D 5L (Herdman *et al.*, 2011)

Fatigue using a Visual Analogue Scale to enable people with aphasia to also rate their level of fatigue (Kersten, Küçükdeveci & Tennant, 2012)

Responsiveness of the outcome measures will also be examined to inform selection of the primary outcome, and to refine the number of secondary outcomes (Tables 15 and 16). Responsiveness is defined as the ability of an outcome measure to detect changes over time in the construct to be measured (Mokkink *et al.*, 2010) and will be utilised with caution as the trial is not sufficiently powered to draw reliable conclusions from hypothesis testing. However, it will provide data to gain a better understanding of which outcomes may be of interest to further explore in a fully powered trial, in particular, to identify the most appropriate choice of primary outcome.

Analysis methods

As this is a feasibility trial, it is not suitably powered to be able to support or justify any conclusions regarding treatment effectiveness and efficacy realised from hypothesis testing (Whitehead *et al.*, 2016), and indeed is not the purpose of the trial. As such, the analysis of the results of this trial will not involve formal statistical testing, but rather will be descriptive summarising each group separately and the differences between allocated groups. Percentages and numbers will be used for categorical data and mean (along with 95% confidence interval), standard deviation and range used if data is approximately normally distributed, or median, inter-quartile range and range if data is highly skewed). This will help to inform the details of a fully powered SPIRES RCT.

Missing Data

In the event a participant is not available for the collection of outcome measures, additional visits will be organised to try to capture the missing measures. However, some loss to follow-up is expected over 12 months, given the severity of stroke. The proportion of participants missing each outcome will be summarised for each allocated group and at each time point, with reasons for missing outcomes documented wherever possible. The main analysis of the primary outcome uses Barthel Index and Edmans Activity of Daily Living Index for Stroke which could be missing for several reasons:

1. Participant opts out of trial before follow-up data collection
2. Participant or proxy refuses to participate in collection of measures
3. Participant moves out of the trial geographical area before follow-up data collection
4. Participant is medically unwell or receiving end of life care
5. Participant dies and is withdrawn from the trial.

There is no a priori reason to assume that participants who are lost to follow-up are missing not at random. Therefore, for the primary analysis, no imputation of missing data will be undertaken, and this primary outcome analysis will be based on the complete case/observed outcomes dataset

Other missing data

As above, any missing secondary or demographic data will be noted for consideration in the design of a subsequent full-scale trial.

Statistical Software

The statistical analyses will be undertaken using Statistical Package for the Social Sciences (SPSS) (IBM Corporation, Released 2016) version 24 or higher.

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Figure 1: CONSORT Flow Diagram of participants through SPIRES

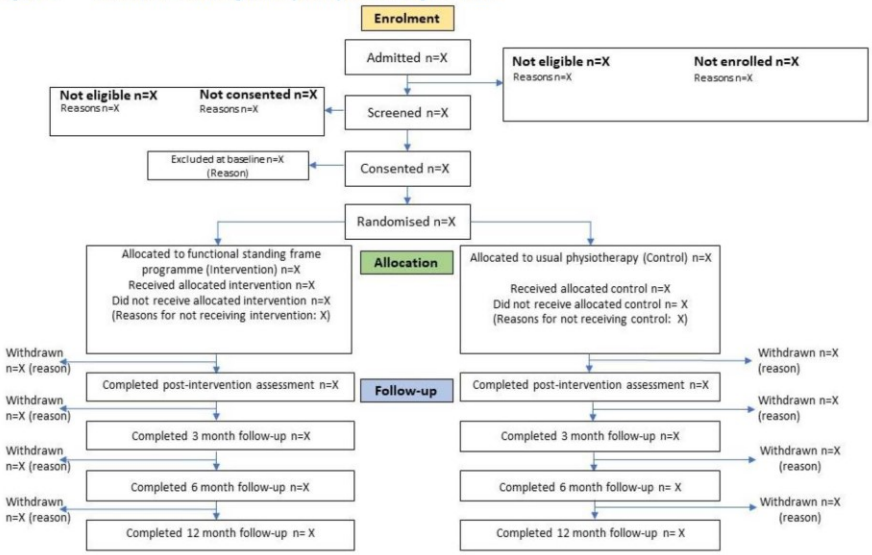


Table 1: Feasibility Objectives

Feasibility Indicator	Outcome Measures	Parameter for Success	Results	Feasible (Y/N)	Suggested Modification
Process					
Recruitment rate	% of participants recruited/time	≥ 70% of 50 participants over 13 months	Calculations shown in Section 3, Trial Objectives		
Retention rate	% of participants completed T1, T2, T3, T4, T5	Complete T2, T3, T4, T5 ≥80%			
Ability to consent	% of participants consenting				
Consent rate	% of consultee declarations				
Eligibility criteria	% of admissions screened & eligible				
Willingness of physiotherapists to recruit	% of admissions screened & approached	≥50% of admissions screened & ≥75% of eligible participants approached ≤10% of participants approached			
Willingness of patients to be randomised	% of participants who refuse to enrol in the trial	≤10% of participants approached			
Acceptability of the intervention	% of withdrawals	≤20% of participants approached			
Determining usual physiotherapy	Frequency specific physiotherapy interventions are implemented	0% functional standing frame programme (e.g. ≥5 sessions per week, ≥8 repetitions of sit to stand and standing for 30 minutes)			
Resources					
Burden	% of participants refusing physiotherapy sessions and follow-up assessments	≤20% of participants recruited			
Cost effectiveness	n= duration (minutes) of functional standing frame programme session				
Management					
Fidelity	Observe intervention and control group sessions	≥3 out of the four Stroke Rehab Units			
Participant adherence	n= sessions per week	≥5 sessions per week or ≥15 sessions over 3-weeks.			
	n= minutes in standing				
	n= sit to stand repetitions				
	Yes; n= No for enjoyment				
	Score out of 10 for effort				
	Score out of 10 for fatigue	≥50% unable to undertake the functional standing frame programme			
Orthostatic hypotension protocol	% incident of orthostatic hypotension % of incomplete sessions due to orthostatic hypotension (OH)	≥50% of participants with OH unable to undertake the functional standing frame programme			
Safety					
Intervention	n= AE & SAE	0% AE*; 0% SAE*			
Data collection	n= AE & SAE	0% AE*; 0% SAE*			

* unexpected and related specifically to the functional standing frame intervention. Baseline (T1), post 3-week intervention (T2), 15 weeks post-randomisation (T3), 29 weeks post-randomisation (T4) and 55 weeks post-randomisation (T5).

Table 2: Adherence to allocated treatment

Adherence Measure		
	n (%) per participant	
Number of sessions attended out of 21	**Intervention Group**	**Control Group**
21 20 19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0		
Number of minutes in standing (target is 30 minutes) for intervention group	**n (%) per participant**	
>30 30 25 20 15 10 5 0		
Number of minutes in usual physiotherapy (target is 15 minutes) for intervention group	**n (%) per participant**	
>15 15 14 13 12 11 10 9 8 7 6 5 4		

3 2 1 0		
Number of repetitions of sit to stand (target is 8-12) for intervention group	**n (%) and median (IQR) per participant**	
>12 12 11 10 9 8 7 6 5 4 3 2 1 0		
Complete Adherence (minimum 5 sessions per week, 30 minutes using the standing frame and 15 minutes of usual physiotherapy and 8 sit to stand repetitions) for intervention group	**n (%)**	
Yes No		
Reasons for non-adherence	**Mean number of sessions not completed per participant (not mutually exclusive)**	
	Intervention Group	**Control Group**
Fatigue Sepsis Participant declined Infectious condition Musculoskeletal injury Skin damage (e.g. injury or pressure damage) Orthostatic hypotension Staff shortage Early discharge from Stroke Rehab Unit Withdrawn (e.g. patient/relative or physio decision) Died Other		
Duration of inpatient stay (days)	**n (%)**	
	Intervention Group	Control Group
Over 21 21 20 19 18 17 16 15 14		

13 12 11 10 9 8 7 6 5 4 3 2 1		
Enjoyment	**Yes (enjoyed)**	**No (did not enjoy)**
Effort	**n (%) per participant**	
None (0) Mild (1-3) Moderate (4-6) Severe (7-9) Unbearable (10)		
Fatigue	**n (%) per participant**	
Not at all (0) A little tired (1-3) Tired (4-6) Really tired (7-9) So tired I can't do anything (10)		
Aches and pains	**n (%) per participant**	
None (0) Mild (1-3) Moderate (4-6) Severe (7-9) Worst pain possible (10)		

Table 3: Serious Adverse Events

Outcome	Functional Standing Frame Programme		Usual Physiotherapy	
	Count and % of SAEs (Calculated by number of SAEs divided by total number of participants)	Count and % of participants with SAEs (Calculated by number of people with SAEs divided by total number of participants)	Count and % of SAEs (Calculated by number of SAEs divided by total number of participants)	Count and % of participants with SAEs (Calculated by number of people with SAEs divided by total number of participants)
Respiratory, thoracic and mediastinal disorders				
Renal and urinary disorders				
Nervous system disorders				
Skin and subcutaneous tissue disorders				
Gastrointestinal disorders				
Blood and the lymphatic system disorders				
Orthostatic hypotension				
Fall				
Injury, poisoning and procedural complications				
Cardiac disorders				
Musculoskeletal and connective tissue disorders				
Metabolism and nutrition disorders				
Ear and labyrinth disorders				
Hepatobiliary disorders				
Congenital and familial and genetic disorders				
General disorders and admin site conditions				
Surgical and medical procedures				
End of life care				
Died				

Table 4: Adverse events

Outcome	Functional Standing Frame Programme		Usual Physiotherapy	
	Count and % of AEs (Calculated by number of AEs divided by the total number of participants)	Count of participants with AEs and % (Calculated by number of people with AEs divided by total number of participants)	Count and % of AEs (Calculated by number of AEs divided by total number of participants)	Count and % of participants with AEs (Calculated by number of people with AEs divided by total number of participants)
Respiratory, thoracic and mediastinal disorders				
Renal and urinary disorders				
Nervous system disorders				
Skin and subcutaneous tissue disorders				
Gastrointestinal disorders				
Blood and the lymphatic system disorders				
Orthostatic hypotension				
Fall				
Injury, poisoning and procedural complications				
Cardiac disorders				
Musculoskeletal and connective tissue disorders				
Metabolism and nutrition disorders				
Ear and labyrinth disorders				
Hepatobiliary disorders				
Congenital and familial and genetic disorders				
General disorders and admin site conditions				
Surgical and medical procedures				
End of life care				
Died				

Table 5: Relatedness of AEs and SAEs to the functional standing frame programme

	Adverse Events		Serious Adverse Events	
	Related	Unrelated	Related	Unrelated
Moderately severe stroke (mRS 4)	%	%	%	%
Very severe stroke (mRS 5)	%	%	%	%

Table 6: Minimisation Characteristics in Allocated Groups

Characteristic	Intervention Group (n=X)	Control Group (n=X)
Fatigue	% with a score 0-3 (no or minimal fatigue) or 4-10 (fatigue)	% with a score 0-3 (no or minimal fatigue) or 4-10 (fatigue)
Orthostatic Hypotension	% with orthostatic hypotension	% with orthostatic hypotension

Table 7: The extent to which the assessor remained blinded

Follow-up Time point post-randomisation	Number of assessments completed	Number (%) of instances the blinded assessor believes they have been unblinded	Number (%) of instances the blinded assessor correctly guessed group allocation
3 weeks			
15 weeks			
29 weeks			
55 weeks			

Table 8: Timing of outcome assessments

Completion status	Baseline (n) (T1)	Post-intervention (T2) (n)	15 weeks follow-up (T3) (n)	29 weeks follow-up (T4) (n)	55 weeks follow-up T5) (n)
Completed within 7 days of consent or ± 7 days from the follow-up visit date as per database(Logan *et al.*, 2018)	%	%	%	%	%
Completed within +/- 8-14 days of consent or ± 7 days from the follow-up visit date as per database (Logan *et al.*, 2018)	%	%	%	%%	%
Not completed	%	%	%	%	%

Table 9: Adherence by site for functional standing frame programme

	Stroke severity	Site 01	Site 02	Site 03	Site 04
Number of sessions completed	mRs 4				
	mRS 5				
Number of minutes in standing	mRs 4				
	mRS 5				
Number of sit to stand repetitions	mRs 4				
	mRS 5				

Figure 2: Relationship between adherence, orthostatic hypotension, fatigue and proposed primary outcome measures (Illustrative plot to be inserted)

Table 10: Baseline and Demographic Data

	Functional standing frame programme (n=)	Usual Physiotherapy (n=)	All (n=)
Age, Mean (SD) [range]			
Gender (%)			
Male			
Female			
Weight in kg, mean (SD) [range]			
Marital Status (%)			
Single			
Married or in a civil partnership			
Separated			
Divorced			
Widowed			
Place of Residence (%)			
Lives at home			
Lives in residential Care			
Other			
Living Arrangements (%)			
Alone			
Spouse/Partner			
Parent(s)			
Children under 18			
Children over 18			
Other family			
Non-family			
Employment Status (%)			
In employment or self-employed			
Retired			
Housework			
Student			
Unemployed			
Other			
Pre-admission modified Rankin Scale, %			
0 (no symptoms)			
1 (no significant disability)			
2 (slight disability)			
3 (moderate disability)			
4 (moderately severe disability)			
5 (severe disability)			
6 (Dead)			
Pre-admission mobility status (%)			
Walking without an aid			
Walking with an aid			
Walking with physical assistance			
Mechanical aid with assistance			
Medical and surgical conditions (%)			
Osteoarthritis – has/had this condition			

Osteoarthritis – ongoing at study entry			
Joint replacement – has/had this condition			
Joint replacement – ongoing at trial entry			
Osteoporosis – has/had this condition			
Osteoporosis – ongoing at trial entry			
Coronary heart disease/ Hypertension/Hypotension – has/had this condition			
Coronary heart disease/ Hypertension/Hypotension – ongoing at trial entry			
COPD/Asthma – has/had this condition			
COPD/Asthma – ongoing at trial entry			
Diabetes – has/had this condition			
Diabetes – ongoing at trial entry			
Depression/anxiety – has/had this condition			
Depression/anxiety – ongoing at trial entry			
TIA – has/had this condition			
TIA – ongoing at trial entry			
Epilepsy/seizure – has/had this condition			
Epilepsy/seizure – ongoing at trial entry			
Neurological condition – has/had this condition			
Neurological condition – ongoing at trial entry			
Other – ongoing at trial entry			
Has Previous strokes (%)			
For those with previous stroke, median (IQR) number of strokes			
Current mobility status (%)			
Hoist			
Transfer board			
Handling belt			
Electronic standing aid			
Mechanical standing aid			
Other			
How many people required?			
Stroke Severity (%)			
NIHSS			
0 (no stroke symptoms)			
1-4 (minor stroke)			
5-15 (moderate stroke)			
16-20 (moderate to severe stroke)			
21-42 (severe stroke)			
mRS			
0 (no symptoms)			

1 (no significant disability)			
2 (slight disability)			
3 (moderate disability)			
4 (moderately severe disability)			
5 (severe disability)			
6 (dead)			
Stroke Classification (%)			
TACS			
PACS			
POCS			
LACS			
Lesion Location (%)			
Cortical			
Middle cerebral artery			
Frontal			
Sub-cortical			
Thalamus			
Basal ganglia			
Midbrain			
Pons			
Medulla			
Cerebellum			
Brain stem			
Parietal			
Temporal			
Occipital			
Stroke sub-type (%)			
Lacunar			
Anterior cerebral artery			
Posterior cerebral artery			
Basilar artery			
Cerebellar artery			
Carotid artery			
Other (e.g. carotid dissection or undetermined)			
Days since stroke admitted to Stroke Rehabilitation Unit, median (IQR)			
Days since stroke informed consent received, median (IQR)			
Prevalence of aphasia (%)			
Prevalence of orthostatic hypotension (%)			
Prevalence of fatigue (%)			
0 (no fatigue) 1-3 (a little tired) 4-6 (tired) 7-9 (really tired) 10 (too tired to do anything)			

Table 11: Summary of Missing Data

Outcome Variable	Completeness of Outcome Measure (n) %	Reason for Missing Data (n) % over all timepoints				
		Declined	Aphasia	Cognitive	Unwell	Died
Barthel Index *Feeding* *Bathing/Grooming/Dressing* *Bladder/Bowels/Toilet use* *Mobility/Transfers/Stairs*						
Edmans Activities of Daily Living Index for Stroke *Washing/Grooming/Dressing* *Meal Times* *Basic Mobility* *Advanced Mobility* *Bed Mobility* *Kitchen Activities* *Housework Activities* *Associated problems:* *Language* *Perceptual* *Sensory* *Dyspraxia* *Reasoning* *Memory* *Depression* *Anxiety* *Urinary continence* *Faecal continence*						
PHQ-9 *Participant has aphasia* *Little interest or pleasure in things* *Feeling down, depressed, hopeless* *Trouble falling asleep or sleeping too much* *Feeling tired or little energy* *Poor appetite or over eating* *Feeling bad about self* *Trouble concentrating on things* *Moving and speaking slowly* *Thoughts of being better off dead/hurting self* *Level of difficulty*						
SAD-Q10 *Weeping spells* *Restless disturbed nights* *Avoid eye contact* *Burst into tears* *Suffer from aches and pain* *Get angry* *Participate in social activities* *Gets restless and fidgety* *Sits without doing anything* *Occupied during the day*						

SAQoL-39 *Preparing food* *Getting dressed* *Taking a bath* *Walking* *Keeping balance when bending* *Climbing stairs* *Walking without stopping to rest* *Standing* *Getting out of a chair* *Doing daily housework* *Finished jobs you started* *Writing or typing* *Putting on socks* *Doing buttons* *Doing a zip* *Opening a jar* *Speaking* *Speaking clearly to use phone* *Getting people o understand you* *Finding word you wanted to say* *Getting people to understand when repeat self* *Write things down to remember them* *Hard to make decisions* *Feel irritable* *Feel personality changed* *Feel discouraged about future* *No interest in people or activities* *Feel withdrawn from people* *Have little confidence in self* *Feel tired most of time* *Stop and rest often during day* *Tired to do what you wanted to* *Feel you were burden to family* *Language interfered with family life* *Gou out less often* *Do hobbies and recreational less often* *See friends less often* *Physical condition interfered with social life* *Language problems interfered with social life* *Physical Score* *Communication Score* *Psychosocial Score* *Energy Score* *Mean Score*							
EQ-5D-5L *Mobility*							

Self-care *Usual Activities* *Pain & discomfort* *Anxiety & depression* *Health state Score*							
Muscle strength *Quadriceps* ***Trial 1 left*** ***Trial 1 right*** ***Trial 2 left*** ***Trial 2 right*** ***Trial 3 left*** ***Trial 3 right***							
Joint Range of Movement *Hip flexion angle* *Left* *Right* *Popliteal angle* *Left* *Right* *Ankle plantar flexion* *Left* *Right* *Ankle dorsal flexion* *Left* *Right*							
Modified Ashworth Scale *Hip adductors* *Left* *Right* *Hamstrings* *Left* *Right* *Ankle flexion* *Left* *Right* *Ankle extension* *Left* *Right*							
Trunk Control Test *Rolling to weak side* *Rolling to strong side* *Balance in sitting position* *Sitting up for lying down* Total score							

Declined = "declined to answer"; aphasia = "unable to answer due to aphasia"; Cognitive = "unable to answer due to cognitive impairment"; Unwell = "unable to answer due to medically unwell"; Died = "Participant died and subsequently withdrawn from the trial".

Table 12: Proposed Primary Outcome Data

		Time point

Outcome variable	Treatment Arm	Baseline (n=xx)	3 (+/-1) weeks (n=xx)	15 weeks (+/-1 week) (n=xx)	29 weeks (+/-1 week) (n=xx)	55 weeks (+/-1 week) (n=xx)
Barthel Index Mean (SD)[range]	*Functional Standing Frame Programme*	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)
	Usual Physiotherapy	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)
Edmans Activities of Daily Living Index for Stroke Mean (SD)[range]	*Functional Standing Frame Programme*	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)
	Usual Physiotherapy	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)

Table 13: Patient and/or Proxy Responses for Potential Primary Outcome Data

Outcome Measure	Time point									
	Baseline (n=xx)		3 (+/-1) weeks (n=xx)		15 weeks (+/-1 week) (n=xx)		29 weeks (+/-1 week) (n=xx)		55 weeks (+/-1 week) (n=xx)	
	Patient	*Proxy*	*Patient*	*Proxy*	*Patient*	*Proxy*	*Patient*	*Proxy*	*Patient*	*Proxy*
Barthel Index	%	%	%	%	%	%	%	%	%	%
Edmans Activities of Daily Living Index for Stroke	%	%	%	%	%	%	%	%	%	%

Table 14: Proposed Secondary Outcomes

Outcome variable	Treatment Arm	Time point				
		Baseline (n=xx)	3 weeks (+/-1) (n=xx)	15 weeks (+/-1 week) (n=xx)	29 weeks (+/-1 week) (n=xx)	55 weeks (+/-1 week) (n=xx)
Muscle length using manual goniometry, Median (IQR) *Hip flexor* *Left* *Right* *Hamstrings* *Left* *Right* *Ankle plantar flexors* *Left* *Right* *Ankle dorsiflexors* *Left* *Right*	*Functional Standing Frame Programme*	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)
Hip flexors *Left* *Right* *Hamstrings* *Left* *Right* *Ankle plantar flexors* *Left* *Right* *Ankle dorsiflexors* *Left* *Right*	*Usual Physiotherapy*	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)
Knee muscle strength measured in Newtons (Maximum score of three trials), Median (IQR)	*Functional Standing Frame Programme*	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)

Knee muscle strength measured in Newtons (Maximum score of three trials), Median (IQR)	*Usual Physiotherapy*	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)
Modified Ashworth Scale Score, Median (IQR) *Hip adductors* *Left* *Right* *Hamstrings* *Left* *Right* *Ankle flexion* *Left* *Right* *Ankle extension* *Left* *Right*	*Functional Standing Frame Programme*	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)
Modified Ashworth Scale Score, Median (IQR) *Hip adductors* *Left* *Right* *Hamstrings* *Left* *Right* *Ankle flexion* *Left* *Right* *Ankle extension* *Left* *Right*	*Usual Physiotherapy*	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)
Trunk Control Test, Median (IQR) Roll to weak side	*Functional Standing*	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)

Roll to strong side Balance in sitting Sit up from lying down	*Frame Programme*					
Trunk Control Test, Median (IQR) Roll to weak side Roll to strong side Balance in sitting Sit up from lying down	*Usual Physiotherapy*	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)
Patient Health Questionnaire 9 (PHQ-9), Median (IQR)	*Functional Standing Frame Programme*	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)
Patient Health Questionnaire 9 (PHQ-9), Median (IQR)	*Usual Physiotherapy*	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)
Stroke Aphasia Depression Questionnaire (SAD-Q10), Median (IQR)	*Functional Standing Frame Programme*	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)
Stroke Aphasia Depression Questionnaire (SAD-Q10), Median (IQR)	*Usual Physiotherapy*	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)
Stroke and Aphasia Quality of Life Scale (SAQOL39), Median (IQR) Physical Psychosocial Communication	*Functional Standing Frame Programme*	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)
Stroke and Aphasia Quality of Life Scale (SAQOL39), Median (IQR) Physical Psychosocial Communication	*Usual Physiotherapy*	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)
European Quality of Life-5 Dimensions (EQ-5D 5L), Median (IQR) *0 (no problems)* *1 (slight problems)*	*Functional Standing Frame Programme*	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)

2 (moderate problems) *3 (severe problems)* *4 (extreme problems/unable)* *Health score (0=worst, 100=best)*						
European Quality of Life-5 Dimensions (EQ-5D 5L), Median (IQR) *0 (no problems)* *1 (slight problems)* *2 (moderate problems)* *3 (severe problems)* *4 (extreme problems/unable)* *Health score (0=worst, 100=best*	*Usual Physiotherapy*	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)	Xx(xx)

Table 15: Percentage change in Proposed Primary Outcome Data from baseline

Outcome variable	Treatment Arm	Time point			
		3 (+/-1) weeks (n=X)	15 weeks (+/-1 week) (n=X)	29 weeks (+/-1 week) (n=X)	55 weeks (+/-1 week) (n=X)
Barthel Index % change	Functional Standing Frame Programme	X(SD)	X(SD)	X(SD)	X(SD)
	Usual Physiotherapy	X(SD)	X(SD)	X(SD)	X(SD)
Edmans Activities of Daily Living Index for Stroke % change	Functional Standing Frame Programme	X(SD)	X(SD)	X(SD)	X(SD)
	Usual Physiotherapy	X(SD)	X(SD)	X(SD)	X(SD)

Table 16 Percentage change in Proposed Secondary Outcome Data from baseline

Outcome variable	Treatment Arm	Time point			
		3 weeks (+/-1) (n=X)	15 weeks (+/-1 week) (n=X)	29 weeks (+/-1 week) (n=X)	55 weeks (+/-1 week) (n=X)
Muscle length using manual goniometry % change *Hip flexor* *Left* *Right* *Hamstrings* *Left* *Right* *Ankle plantar flexors* *Left* *Right* *Ankle dorsiflexors* *Left* *Right*	*Functional Standing Frame Programme*	X(SD)	X(SD)	X(SD)	X(SD)
Hip flexors *Left* *Right* *Hamstrings* *Left* *Right* *Ankle plantar flexors* *Left* *Right* *Ankle dorsiflexors* *Left* *Right*	*Usual Physiotherapy*	X(SD)	X(SD)	X(SD)	X(SD)
Knee muscle strength measured in Newtons (Maximum score of three trials) *% change*	*Functional Standing Frame Programme*	X(SD)	X(SD)	X(SD)	X(SD)

Knee muscle strength measured in Newtons (Maximum score of three trials) *% change*	*Usual Physiotherapy*	X(SD)	X(SD)	X(SD)	X(SD)
Modified Ashworth Scale Score *% change* *Hip adductors* *Left* *Right* *Hamstrings* *Left* *Right* *Ankle flexion* *Left* *Right* *Ankle extension* *Left* *Right*	*Functional Standing Frame Programme*	X(SD)	X(SD)	X(SD)	X(SD)
Modified Ashworth Scale Score *% change* *Hip adductors* *Left* *Right* *Hamstrings* *Left* *Right* *Ankle flexion* *Left* *Right* *Ankle extension* *Left* *Right*	*Usual Physiotherapy*	X(SD)	X(SD)	X(SD)	X(SD)
Trunk Control Test *% change* Roll to weak side Roll to strong side Balance in sitting	*Functional Standing Frame Programme*	X(SD)	X(SD)	X(SD)	X(SD)

Sit up from lying down					
Trunk Control Test *% change* Roll to weak side Roll to strong side Balance in sitting Sit up from lying down	*Usual Physiotherapy*	X(SD)	X(SD)	X(SD)	X(SD)
Patient Health Questionnaire 9 (PHQ-9) *% change*	*Functional Standing Frame Programme*	X(SD)	X(SD)	X(SD)	X(SD)
Patient Health Questionnaire 9 (PHQ-9) *% change*	*Usual Physiotherapy*	X(SD)	X(SD)	X(SD)	X(SD)
Stroke Aphasia Depression Questionnaire (SAD-Q10) *% change*	*Functional Standing Frame Programme*	X(SD)	X(SD)	X(SD)	X(SD)
Stroke Aphasia Depression Questionnaire (SAD-Q10) *% change*	*Usual Physiotherapy*	X(SD)	X(SD)	X(SD)	X(SD)
Stroke and Aphasia Quality of Life Scale (SAQOL39) *% change* Physical Psychosocial Communication	*Functional Standing Frame Programme*	X(SD)	X(SD)	X(SD)	X(SD)
Stroke and Aphasia Quality of Life Scale (SAQOL39) *% change* Physical Psychosocial Communication	*Usual Physiotherapy*	X(SD)	X(SD)	X(SD)	X(SD)
European Quality of Life-5 Dimensions (EQ-5D 5L) *% change* *0 (no problems)* *1 (slight problems)* *2 (moderate problems)* *3 (severe problems)* *4 (extreme problems/unable)*	*Functional Standing Frame Programme*	X(SD)	X(SD)	X(SD)	X(SD)

Health score (0=worst, 100=best)					
European Quality of Life-5 Dimensions (EQ-5D 5L) *% change* *0 (no problems)* *1 (slight problems)* *2 (moderate problems)* *3 (severe problems)* *4 (extreme problems/unable)* *Health score (0=worst, 100=best*	*Usual Physiotherapy*	X(SD)	X(SD)	X(SD)	X(SD)

Appendix 6 Treating therapist control group Case Report Form

CONTROL PARTICIPANT STUDY NUMBER ☐☐☐☐☐

Week 1 Session 1 PARTICIPANT INITIALS ☐☐☐

SPIRES

PHYSIOTHERAPY SESSION DETAILS

Session date d d / m m / y y y y

Was session completed? Yes ☐ No ☐

If No, please give reason ☐

Did the participant experience OH? Yes ☐ No ☐

If Yes:

Did the participant receive treatment for OH? Yes ☐ No ☐ N/A ☐

If Yes, what was the treatment? Pharmacological ☐ Non-pharma ☐ N/A ☐

Did hypotension affect completion of session? Yes ☐ No ☐ N/A ☐

Please check for any Adverse Events, and record on the AE pages at the back of this CRF.

Total duration of session (in minutes) ☐

Please continue on next page

CONTROL PARTICIPANT STUDY NUMBER ☐☐☐☐☐

Week 1 Session 1 PARTICIPANT INITIALS ☐☐☐

SPIRES

NO STANDING FRAME

Gross position of patient during treatment activities used:
Please tick all boxes that apply

Supine	☐	Prone	☐	Side lying affected side	☐
Side lying unaffected side	☐	Supported sitting	☐	Supported standing	☐
Perch sitting	☐	Unsupported sitting	☐	Unsupported standing	☐
Prone standing	☐	4-point kneeling	☐	2-point kneeling	☐
Crook lying	☐				

Treatment activities:
Please tick all boxes that apply

Exercise to increase strength	☐	Exercise to increase cardiovascular fitness	☐	Exercise to improve co-ordination	☐
Upper limb tasks	☐	Facilitation of movement /muscle activation	☐	Soft tissue mobilisation	☐
Joint mobilisation	☐	Sensory stimulation	☐	Balance activities (static)	☐
Balance activities (dynamic)	☐	Functional tasks (e.g. sit to stand, wash/dress)	☐	Practising transfers	☐
Stepping/walking/ gait re-education	☐	Review/progress seating	☐	Positioning	☐
Tone management	☐	Oedema management	☐	Pain management	☐
Splinting techniques	☐	Orthotics	☐	Education/training for patient and family	☐

Other treatment activities:
Please tick all boxes that apply

Acupuncture	☐	Taping (e.g. ROCK/Kinesio Tape)	☐	Ultrasound	☐
Compression	☐	Warm water bathing	☐	Body weight support treadmill training	☐
Functional electrical stimulation	☐	Microstim	☐	Hydrotherapy	☐
Theraband	☐	Nintendo Wii or other virtual reality games	☐	Lycra/compression garments	☐
Other treatment (please specify)	☐				

COMPLETED BY (CAPITALS) ☐

SIGNATURE ☐ DATE d d / m m / y y y y

Pages 2 and 3 represent one session and are repeated in the CRF to provide 21 sessions.

Appendix 7 Screening Case Report Form

SCREENING PARTICIPANT STUDY NUMBER ☐☐☐☐☐

PARTICIPANT INITIALS ☐☐☐

SPIRES

Date of screening d d / m m / y y y y

DEMOGRAPHICS

Gender Male ☐ Female ☐

Date of birth d d / m m / y y y y

NATIONAL INSTITUTES OF HEALTH STROKE SCALE (NIHSS)

Please circle ONE answer

0	No stroke symptoms
1 - 4	Minor stroke
5 - 15	Moderate stroke
16 - 20	Moderate to severe stroke
21 - 42	Severe stroke

MODIFIED RANKIN SCALE (mRS)

Please circle ONE answer

0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

Please now consider the following inclusion and exclusion criteria for the study

INCLUSION CRITERIA	**Yes**	**No**
1) Has a new (first/recurrent) clinical diagnosis of stroke, cerebral haemorrhage or infarct confirmed by consultant or CT scan leading to admission to the SRU	☐	☐
2) Aged ≥18 years	☐	☐
3) Graded as mRS 4 or 5 and/or NIHSS≥16 (severe or very severe stroke and unable to stand without support/mechanical aid and assistance of two people)	☐	☐
4) Able to give informed consent or assent received from a consultee (see recruitment section)	☐	☐
5) Conscious and responsive to verbal commands.	☐	☐

If the answer to any of the INCLUSION CRITERIA is NO the participant is NOT eligible for inclusion in the study

EXCLUSION CRITERIA	**Yes**	**No**
1) Systolic blood pressure ≤100mmHg or ≥220mmHg at rest lying or sitting	☐	☐
2) Oxygen saturation ≤87% with or without supplementary oxygen (e.g. severe acute/chronic cardiorespiratory disease)	☐	☐
3) Resting heart rate of ≤40 or ≥110 beats per minute (e.g. cardiovascular instability)	☐	☐
4) Temperature ≥38.5 degrees centigrade or ≤35 degrees centigrade	☐	☐
5) Orthopaedic impairments which prevent full weight bearing in standing	☐	☐
6) Malnutrition Universal Screening Tool score of ≥2, or deemed to be not meeting nutritional demands for therapeutic interventions by dietician	☐	☐
7) Documented clinical decision for receiving end of life care	☐	☐
8) Unstable coronary or other medical condition that is judged by the PI/CI or clinical team to impose a medical risk to the patient by involvement in the study	☐	☐
9) Assessed functionally by specialist clinicians as being a risk to themselves or others due to their inability to follow non-verbal prompts or are behaving erratically	☐	☐
10) Immobile and not weight bearing pre-stroke	☐	☐
11) Additional neurological deficits unrelated to the current or past stroke (e.g. peripheral neuropathy or Multiple Sclerosis)	☐	☐
12) Weight of 115kg or more	☐	☐
13) Being discharged out of county	☐	☐
14) Already actively participating in a research study that the CI considers might conflict with this trial	☐	☐
15) Non-English speaking.	☐	☐

If the answer to any of the EXCLUSION CRITERIA is YES the participant is NOT eligible for inclusion in the study

CONSENT

Date of consent of participant d d / m m / y y y y

Or, if a participant is deemed to lack capacity they will be included in the study if a consultee provides written assent

Date of consent of consultee d d / m m / y y y y

THE PRINCIPAL INVESTIGATOR OR OTHER AUTHORISED CLINICIAN MUST SIGN BELOW TO CONFIRM PARTICIPANT'S ELIGIBILITY

CONFIRMED BY (CAPITALS):

SIGNATURE: **DATE:** d d / m m / y y y y

Please now (for eligible and consented participants):

- Register the participant on the SPIRES website (http://penctu.psmd.plymouth.ac.uk/spires)
- The registration process will provide the participant's study number. Please add this to the front of this document and the top of all pages
- Add participant's study number to the Approach Log
- Create a participant study folder (add study number to new folder)

IF POSSIBLE THE MINIMISATION ASSESSMENTS, ON THE FOLLOWING PAGES, NEED TO BE TAKEN DIRECTLY AFTER CONSENT

If minimisation assessments are not going to be completed now:

- File this document in the participant study folder

MINIMISATION ASSESSMENTS

BLOOD PRESSURE

Instructions:

1) Do not use automated equipment – use a manual sphygmomanometer
2) The participant will be lying down for at least five minutes
3) Ensure the cuff size is appropriate for the participant. Measure blood pressure. Leave the cuff in place
4) Participant assisted into upright sitting (chair or bed)
5) **Immediately** take blood pressure
6) Repeat readings at 1 minute, 3 minutes and 5 minutes

Please record blood pressure for the five timepoints below

Blood pressure lying down	☐	/ ☐	mm Hg
Blood pressure once sat up	☐	/ ☐	mm Hg
Blood pressure sitting up at 1 minute	☐	/ ☐	mm Hg
Blood pressure sitting up at 3 minutes	☐	/ ☐	mm Hg
Blood pressure sitting up at 5 minutes	☐	/ ☐	mm Hg

Did the participant experience light-headedness or dizziness? Yes ☐ No ☐

A DROP IN SYSTOLIC BLOOD PRESSURE OF ≥20 mm Hg BETWEEN TWO TIMEPOINTS, OR A DROP IN DIASTOLIC BLOOD PRESSURE OF ≥10 mm HG BETWEEN TWO TIMEPOINTS, OR EXPERIENCING LIGHT-HEADEDNESS OR DIZZINESS IS CONSIDERED ORTHOSTATIC HYPOTENSION.

Please tick one of the boxes below

No hypotension ☐ Orthostatic hypotension ☐

FATIGUE ASSESSMENT

Using the scale on the laminated card, please tick ONE answer and if possible record the actual score

(0-3) No or minimal fatigue ☐ (4-10) Fatigue ☐

Optional: What was the actual score eg 6, or the range eg Tired or 4-6 ☐

THE ASSESSOR OR PRINCIPAL INVESTIGATOR OR OTHER AUTHORISED CLINICIAN MUST SIGN BELOW TO CONFIRM PARTICIPANT'S MINIMISATION ASSESSMENTS HAVE BEEN COMPLETED

COMPLETED BY (CAPITALS): ☐

SIGNATURE: ☐ **DATE:** d d / m m / y y y y

PI or Authorised Clinician, please now:

- **Photocopy all pages and file the original and copy in the participant's study folder. The Assessor will collect the original during their baseline visit**

Assessor, please now:

- **Log on to the SPIRES website (http://penctu.psmd.plymouth.ac.uk/spires) and randomise this participant**
- **Photocopy all pages and file the copy in the participant's study folder and collect the original during their baseline visit**

Appendix 8 Post-screening Case Report Form

POST SCREENING PARTICIPANT STUDY NUMBER ☐☐☐☐☐

PARTICIPANT INITIALS ☐☐☐

SPIRES

DEMOGRAPHIC DATA

Weight ☐☐☐ Kg

Marital status

Single (never married or civil partnered)	☐	Separated (but still legally married or in a civil partnership)	☐
Married or in a civil partnership	☐	Divorced or civil partnership dissolved	☐
		Widowed or surviving civil partner	☐

Which of the following best describes the patient's current living situation?

Please tick one box only

Lives at home	☐	In residential care	☐
Other	☐		

If Other, please specify below:

☐

Who does the participant live with?

Please tick all boxes that apply

Lives alone	☐	Children under 18	☐
Spouse/partner	☐	Children over 18	☐
Parent(s)	☐	Other family	☐
		Non-family	☐

Which of the following best describes the patient's main activity?

Please tick one box - If the patient qualifies for more than one category the occupation involving the most hours should be recorded

In employment or self-employment	☐	Retired	☐
Housework	☐	Student	☐
Unemployed	☐	Other	☐

If Other, please specify below:

☐

PRE-ADMISSION MODIFIED RANKIN SCALE

BEFORE ADMISSION, which of the following best described the participant's disability status?

Please circle ONE answer

0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

PRE-ADMISSION MOBILITY STATUS

BEFORE ADMISSION, what was the participant's lowest level of mobility?

Please tick one box only

Walking without an aid	☐	Walking with physical assistance	☐
Walking with an aid	☐	Mechanical aid with assistance	☐

MEDICAL HISTORY

Record below the details of any significant medical history

Medical and surgical conditions	Has/had this condition? YES	NO	Ongoing at study entry? YES	NO
Osteoarthritis	☐	☐	☐	☐
Joint replacement	☐	☐		
If Yes, please specify:				
Osteoporosis	☐	☐	☐	☐
Coronary heart disease/Hypertension/Hypotension	☐	☐	☐	☐
COPD/asthma	☐	☐	☐	☐
Diabetes	☐	☐	☐	☐
Depression/anxiety	☐	☐	☐	☐
TIA	☐	☐		
Epilepsy/seizure	☐	☐	☐	☐
Neurological condition	☐	☐	☐	☐

Please include details of any other conditions (including other neurological conditions) below

Other medical and surgical conditions		Ongoing at study entry? YES	NO
1		☐	☐
2		☐	☐
3		☐	☐
4		☐	☐
5		☐	☐
6		☐	☐
7		☐	☐

Previous strokes

Has the participant had any previous strokes? Yes ☐ No ☐

If Yes, how many strokes?

The following questions relate to the most recent stroke only:

Date of stroke d d / m m / y y y y

Date of admission to SRU d d / m m / y y y y

OXFORD STROKE CLASSIFICATION

What is the participant's Oxford Stroke Classification?

Note: Oxford Stroke Classification is also known as Bamford Classification

TACS	Total Anterior Circulation Stroke	☐
PACS	Partial Anterior Circulation Syndrome	☐
POCS	Posterior Circulation Syndrome	☐
LACS	Lacunar Syndrome (LACS)	☐

LESION LOCATION

Describe the participant's lesion location according to the CT brain report

Please tick all boxes that apply

Frontal ☐	Parietal ☐	Occipital ☐
Temporal ☐	Brain Stem ☐	Basal Ganglia ☐
Medulla ☐	Pons ☐	Cerebellum ☐
Midbrain ☐	Thalamus ☐	
Middle Cerebral Artery ☐	Anterior Cerebral Artery ☐	Posterior Cerebral Artery ☐
Basilar Artery ☐	Cerebellar Artery ☐	Carotid Artery ☐
Lacunar ☐		
Other ☐		

If Other, please specify below:

TRANSFER STATUS

Equipment required for transfer from bed to chair

Please tick all boxes that apply

Hoist	☐	Electronic standing aid	☐
Transfer board	☐	Mechanical standing aid	☐
Handling belt	☐	Other	☐

If Other, please specify below:

How many people required? ☐

Any other resources?

STROKE APHASIC DEPRESSION QUESTIONNAIRE

Does the participant have aphasia? Yes ☐ No ☐

IF YES, please complete the Stroke Aphasic Depression Questionnaire below.
IF NO, please leave the questionnaire below blank and proceed to the VISIT SIGN OFF

In the last 7 days….	All 7 days	On 4 - 6 days	On 1 - 3 days	Not at all
Did he/she have weeping spells?	☐	☐	☐	☐
Did he/she have restless disturbed nights?	☐	☐	☐	☐
Did he/she avoid eye contact when you spoke to him/her?	☐	☐	☐	☐
Did he/she burst into tears?	☐	☐	☐	☐
Did he/she indicate suffering from aches and pains?	☐	☐	☐	☐
Did he/she get angry?	☐	☐	☐	☐
Did he/she refuse to participate in social activities?	☐	☐	☐	☐
Did he/she sit without doing anything?	☐	☐	☐	☐
Did he/she keep him/herself occupied during the day?	☐	☐	☐	☐
Did he/she get restless and fidgety?	☐	☐	☐	☐

VISIT SIGN OFF

COMPLETED BY (CAPITALS)

SIGNATURE DATE d d / m m / y y y y

Please now:

- **Photocopy all pages and file the original and copy in the participant's study folder. The Assessor will collect the original during their baseline visit**

RESEARCH WITH PLYMOUTH UNIVERSITY
NHS National Institute for Health Research

<Local header here>

SPIRES
STANDING PRACTICE IN REHABILITATION EARLY AFTER STROKE

We would like to invite you to take part in our research study

- Before you decide whether to take part it is important for you to understand why the research is being done and what it would involve for you
- Please take time to read the following information carefully
- Please ask us if anything is not clear, or if you would like more information. This study aims to find out if it is possible to carry out a standing frame programme including repeated standing up and sitting down early after a severe stroke.

Key contents

Important information

- If you take part in the study you will be randomly allocated to one of two groups: either the standing frame programme or your usual physiotherapy
- The study involves regular assessments over about a year with a total of eight study visits. Four or five visits will be held at the hospital where you are receiving your Stroke Rehabilitation depending on when you are discharged from hospital. The other visits will be held in your place of residence.

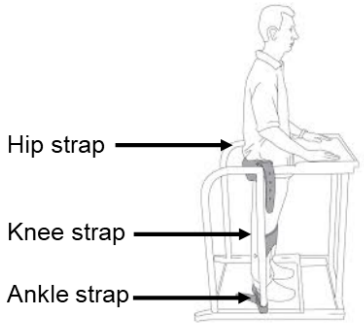
- If you have any questions about this study please contact:
- [Enter name (local Principal Investigator)]
- [Enter telephone number]

Or

Angie Logan
Chief Investigator
01872 256463 or
angie.logan@plymouth.ac.uk

What is a standing frame?

A standing frame can be useful in enabling people with severe stroke to stand safely and securely in a supported position. The electronic power mechanism on the frame can help gradually move people safely from sitting into standing, if they need assistance to do so. Straps at the hips, knees and ankles provide support throughout the stand. There are also straps that can help support your trunk (your body) if you need it once you are standing.



What is the purpose of the study?

- Stroke affects over 152,000 people in the UK every year. People with severe stroke have significant muscle weakness which means they spend much of their time in bed or sitting. This inactivity can cause their muscles to become even weaker and stiff. It may also cause sudden drops in their blood pressure when moving from lying to standing (this is called orthostatic hypotension) which may interfere with their ability to participate in their rehabilitation.
- Currently physiotherapy for people with severe stroke focuses on practising tasks such as getting in and out of bed or a chair. These activities are important for independence and achieving discharge home. Standing up early after a stroke may help strengthen muscles, reduce orthostatic hypotension and minimise or prevent muscles from becoming stiff and weaker. Our research aims to assess whether it is possible for people with severe stroke to use a standing frame to practise functional movements such as standing and moving between sitting and standing.

Why have I been chosen for the study?

You are being invited to take part because you have recently had a stroke which means that you now need assistance from two people and/or some equipment to undertake your daily activities.

What would taking part involve?

We are aim for 50 people with severe stroke to take part in our research from four different stroke rehabilitation units across Cornwall and Devon in the UK. Half of those recruited will take part in the standing frame programme and the other half will receive their usual physiotherapy.

The standing frame programme involves standing and moving between sitting and standing for 30 minutes. Whilst you are standing you will be able to do activities that interest you - play table-top games to encourage your balance and use your arms, reading, or watching television etc. A further 15 minutes will provide time for usual physiotherapy where you may practise using a piece of equipment to help you get in/out of bed or your chair or specific activities that you or your physiotherapist suggests. The usual physiotherapy will involve activities chosen by yourself or guided by your physiotherapist.

- The standing frame programme will be undertaken ideally at least five days per week for three weeks and each session will last a total of 45 minutes
- The usual physiotherapy will be undertaken ideally five days per week for three weeks and each session will last a total of 45 minutes

At the end of every physiotherapy session your physiotherapist will ask you four very simple questions to ask you to rate your level of enjoyment, effort, tiredness and any aches or pains.

If you agree to take part in the study this will involve eight study visits over a period of about a year. Each study visit will include having a number of assessments which will be the same on every visit and be non-invasive.

Who decides which physiotherapy programme I receive?

If you agree to take part in the study, you will be allocated at random (by chance - like tossing a coin) by a computer to receive either the standing frame programme or usual physiotherapy. Once you have been allocated to either the standing frame programme or usual physiotherapy, you will continue to receive the same physiotherapy treatment throughout the study.

Does the standing programme frame have any side effects?

With any therapy there is a possibility of unwanted side effects. Side effects of the standing frame programme may include:

1) Pain or discomfort

Some people experience mild discomfort when they first begin standing such as muscle stiffness, back ache or a stretched feeling in the leg muscles. These are normal and should pass fairly quickly.

2) Orthostatic hypotension

Some people experience dizziness or feeling faint due to a drop in blood pressure . This can happen because your leg muscles are weak and not able to pump the blood back up to your head.

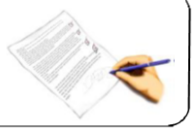
Your physiotherapist and doctor will monitor and manage any side effects. Be reassured however, that standing frames are used by physiotherapists regularly in their work and there are very few risks associated with them. Additionally, the physiotherapists are experienced at working with people with stroke.

Summary of study visits

- Below is a summary of what happens at each visit. The approximately time each visit will take is written in brackets by the title of each box. During all visits you will be able to take a break when you need it.

Study visit 1: agreement to participate (20 minutes)

- We will review your medical records to check that you will be safe and eligible to participate. We will give you information about this research study and answer your questions. You will be asked to sign or tick a form to agree your participation.



Study visit 2: assessments for blood pressure and fatigue (15 minutes)

A healthcare professional will check your blood pressure whilst you are laying down and again once they have helped you sit upright. They will also ask you to score your level of fatigue (tiredness) using a scale of 0-10.

Both of these measures will help the researchers ensure that each of the two physiotherapy groups have a similar amount of people. For example, each of the two physiotherapy groups will have a similar amount of people who have low blood pressure and experience fatigue.

Study visit 3: baseline assessments (60 minutes)

- Assessments.

These include your ability to carry out activities of daily living.

Washing, dressing, getting in and out of a chair or bed and moving around

They will also test your muscles (for strength, length and stiffness) and your balance

Study visit 4: immediately after your physiotherapy programme (60minutes)

- Assessments.

These include your ability to carry out activities of daily living.



Washing, dressing, getting in and out of a chair or bed and moving around

They will also test your muscles (for strength, length and stiffness) and your balance


Study visit 5: after your physiotherapy programme (60 minutes)

- Interviews.

We would like to interview you to find out your experience of the physiotherapy programme as well as understand how you felt about being randomly allocated into one of the two different groups. The interview will last no longer than one hour and will take place within seven days after you have finished the physiotherapy. This may take place in hospital or your place of residence, depending on whether you have been discharged from hospital on the date of the interview. The interview will be digitally voice-recorded and transcribed for data analysis

Study visit 6: 3 months after your physiotherapy programme (60 minutes)

- Assessments.

These include your ability to carry out activities of daily living, such as washing, dressing, getting in and out of a chair bed and moving around. They will also test your muscles (for strength, length and stiffness) and your balance. This visit will be undertaken in your place of residence (e.g. where ever you are living).

These will be the same measures in Study Visits 3 and 4.

Study visit 7: 6 months after your physiotherapy programme (60 minutes)

- Assessments.

These include your ability to carry out activities of daily living, such as washing, dressing, getting in and out of a chair bed and moving around. They will also test your muscles (for strength, length and stiffness) and your balance. This visit will be undertaken in your place of residence (e.g. where ever you are living).

These will be the same measures in Study Visit 6.

Study visit 8: 12 months after your physiotherapy programme (60 minutes)

- Assessments.

These include your ability to carry out activities of daily living, such as washing, dressing, getting in and out of a chair bed and moving around. They will also test your muscles (for strength, length and stiffness) and your balance. This visit will be undertaken in your place of residence (e.g. where ever you are living).

These will be the same measures in Study Visits 6 and 7.

Study visit 1 - screening and consent

At the first visit a member of the research team (the Principal Investigator) will explain what the research study is about. They will answer any questions you may have about the study. If you decide to take part you will be asked to sign a consent form and be given a copy to keep.

Study visit 2 - assessments for blood pressure and fatigue

During this visit a healthcare professional will check your blood pressure and ask you to score your level of fatigue (tiredness). There is a chance that study visits 2 and 3 could be on the same day, but

Study visit 3 - baseline assessments

Your third visit will be immediately before you start your physiotherapy programme.

At this visit you will undergo assessments to provide a baseline from which to compare any progress through the study. Firstly, the physiotherapist will assess your function by asking you questions about your ability to perform activities of daily living. Questions will be about your ability to care for yourself such as washing and dressing, shaving, eating and drinking as well as your ability to get yourself in and out of bed or chair.

You will then undergo some physical assessments. These will include:

- Assessing your muscles to test their strength, length and stiffness
- Assessing your ability to move and maintain your balance whilst sitting down

You can have a rest during these assessments. The physiotherapist will then ask you some questions about fatigue (extreme tiredness as a result of your stroke) and emotions (whether your stroke has affected your emotions/mood, e.g. you are tearful or feel frustrated).

Study visit 4 - immediately after your three week physiotherapy programme

Your fourth visit will be immediately after you have finished your three week physiotherapy programme. At this visit you will repeat all the assessments that you did at the start of the study (study visit 2). The aim of repeating these assessments is to find out how you are now that the study physiotherapy programme has stopped.

Study visit 5 - interviews

During your fifth visit the researcher, Angie Logan, will ask you some questions to find out:

- Your thoughts and feelings about the information you were given before and during the study
- Your thoughts, feelings and experiences of being randomly allocated into one of two physiotherapy programmes
- Your thoughts, feelings and experiences of undertaking the functional standing frame programme (if you were allocated to this group)
- Your thoughts, feelings and experiences about the assessments that you undertook.

You can have a rest during the interview. The interview will take place in a private, quiet location. You can have a family member or carer with you during the interview if you prefer.

The interview will be undertaken by the researcher who is professionally trained in interviewing people and highly skilled in working with people with stroke.

Study visits 6, 7 and 8

Study visits 6, 7 and 8 will be repeating the assessments conducted in study visits 3 and 4. Study visit 8 will be the final visit.

What are the possible disadvantages and risks of taking part?

We don't expect you to be harmed in any way by taking part in this study. There is a possibility that you might experience some side effects - most commonly muscle aches and pains and tiredness. However, these are often short lived. During the interview and some of your study visits you will be asked questions about your experience of your stroke and its impact on your day-to-day life which might be potentially sensitive or upsetting. The researchers and physiotherapists are professionally trained and will ask questions sensitively. You do not have to answer questions which cause you to feel upset. You can also speak to anyone from the research or clinical care team, if you wish to do so.

What are the possible benefits of taking part?

You may or may not benefit directly from this study but by taking part you will be contributing to a study which could potentially bring future benefit to large numbers of people with stroke. If the study results suggest that it is possible for people with severe stroke to undertake a functional standing frame programme as part of their rehabilitation, this will allow us to find out what benefits the programme will have. This may lead to improved rehabilitation programmes for people with severe stroke.

Do I have to take part?

No. Participation is entirely voluntary. It is up to you to decide whether or not to take part in the study. If you decide not to take part, this will not affect the rehabilitation or treatment you receive for your stroke. You do not have to take part and you do not have to give a reason for this. However, if you are willing to share your reasons with the researcher, this will be useful to us when we design other studies in the future.

If you do decide to take part you will be given this information sheet to keep and asked to sign a consent form.

What happens if I don't' want to carry on with the study?

You are free to withdraw from the study at any time without your medical care or legal rights being affected. If you want to withdraw from the study you do not have to give a reason for this; however, if you are willing to give a reason, this will be useful to us when we design other studies in future. If you decide to withdraw from the study at any stage, information collected during the study may still be used unless you ask for it not to be.

What if there is a problem?

Complaints: If you have a concern about any aspect of this study, please speak to someone in your research team or clinical care team who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complains Procedure <add PALS number here>

Harm: We don't expect any harm to come to you as a result of participating in the study. If you are harmed and this is due to someone's negligence than you may have grounds for a legal action for compensation against your hospital's Trust but you may have to pay your legal costs. There are no special compensation arrangements in place. The normal NHS complaints mechanisms will still be able to help you.

Will my taking part in this study be kept confidential?

All information collected about you whilst taking part in this study will be kept strictly confidential and be collected and stored in accordance with the Data Protection Act (1998).

You will be allocated a unique study number which will be used on all documents so that your name is kept confidential. Paper-based information will be stored in locked filling cabinets within a locked office in Peninsula Clinical Trials Unit (PenCTU). Information kept on computers will be stored securely on a system maintained by Plymouth University. Copies of the study information (e.g. your signed Consent Form) will be held securely at your local hospital. Only members of the research team and PenCTU at Plymouth University will have direct access to the study information.

Authorised people from your NHS Trust, PenCTU and the research team may need to review your medical records and the interview transcript to check that the study is being carried out correctly. The Sponsor (Royal Cornwall Hospital NHS Trust) may also need to access the data for audit purposes. Everyone will have a duty of confidentiality to you as a research participant. As part of the consent process, you will be asked to consent to your contact details (name, address, telephone number) being kept by the researcher, Angie Logan, so she can contact you to make appointments for your follow up study visits. These details will be stored separately from the anonymised data at Plymouth University. If you share any information with the researchers which suggests you may be at risk of any harm, this information may be shared with other professionals such as clinical team or your GP.

Will the study information be used to help other research?

It is important that good quality research data can be shared with others in order to advance clinical research and to benefit patients in the future. After the end of the study, de-identified information collected during the study may be made available to other researchers under an appropriate data sharing agreement, but it will not be possible to identify you personally from any information shared.

We will use the information to inform future research to investigate the effectiveness of the functional standing frame programme if the results of this feasibility trial are favourable.

What happens at the end of the study? Will I find out the results?

Once your participation in the study has ended, your usual stroke care will continue as before. When every participant has completed the study, we will prepare the study results (this normally takes several months) and send you a summary of the findings. The study results may be presented at national and international conferences and published in medical journals but you will not be identified

Involvement of your General Practitioner (GP) / family doctor

Your GP will be informed of your participation in this study.

Who is organising and funding the research?

The study is being led by Angie Logan, Clinical Doctoral Research Fellow and Specialist Physiotherapist in stroke rehabilitation. The study is funded by a grant awarded by the National Institute for Health Research. The study will be managed by PenCTU at Plymouth University and overseen by Royal Cornwall Hospitals NHS Trust.

Who has reviewed the study?

All NHS research is looked at by an independent research panel (Research Ethics Committee). The study has been reviewed and given favourable opinion by <enter name> Research Ethics Committee and the Research and Development departments at Cornwall Partnership Foundation NHS and Royal Devon and Exeter.

Appendix 10 Participant information sheet (multiple page for people with aphasia)

SPIRES
STANDING PRACTICE IN REHABILITATION EARLY AFTER STROKE

RESEARCH WITH PLYMOUTH UNIVERSITY

Cornwall Partnership NHS
NHS Foundation Trust

The research story

What is the research?

We are doing some **research**

It is about **practising standing up early after stroke**

Research helps us **learn**

We need to **know** more about **how to help** people **recover after stroke**

Why me?

You have had a **stroke**

Insert photo of each hospital site

You are having **treatment** for your stroke in
<Local Header/Information here>

Who is doing the research?

The research is run from **Plymouth University**

The main **researcher** is **Angie Logan**

NHS
National Institute for Health Research

The **National Institute for Health Research** is **paying** for this research

Why are we doing the research?

Research **tests new ideas** in **physiotherapy**

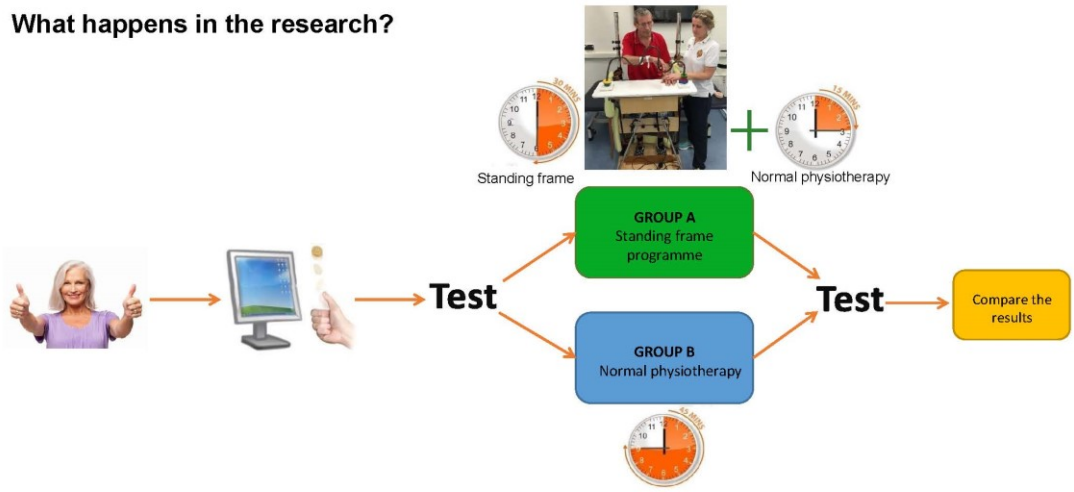
We can find out if **standing up** early after a stroke

and practising **standing up** and **sitting down** helps people **recover**

You will practice standing up and sitting down for **30 minutes**

5 days out of 7

What happens in the research?



There are two groups: A and B

Treatment Group A: standing frame programme for 30 minutes plus 15 minutes of normal physiotherapy

Treatment Group B: normal physiotherapy for 45 minutes

You would **not know which** you get. The **computer decides**. This is like **flipping a coin**

What will I have to do?

Do some **exercises**

have some **assessments**

answer some **questions**

share your **opinions** and **ideas**

	We will take **sound recordings** when we **interview** you This helps us to **remember** what you said
 	**Only the researchers** will **hear** the recordings They will be kept **safe**

Where will the research happen?

Insert photo of each site here	The research will happen in **hospital** <Redruth Hospital> <Bodmin Hospital> <Mount Gould Hospital> <Bideford Hospital>
	A researcher will **visit** you at **home** after you have **left hospital** to **repeat** the **assessments**

How long will the research last?

How long will the research last?  	The **whole research** will last for **3 years** **Your part** will last for **12 months** You will have **appointments** at **3 months**, **6 months** and **12 months** after your physiotherapy.

Will I get paid?

	You will **not get paid** for taking part in the research

Do I have to take part?

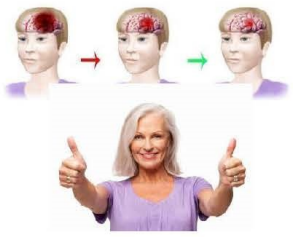
	**You can decide** You **don't have to** You can say **no** If you don't take part you will **still get** your **normal physiotherapy**
 	If you change your mind, **you can stop** at any time You **don't** have to **give a reason** If you **stop** you will still get your **normal physiotherapy**

	You will need to **decide today** if you want to take part. This is **because** the **physiotherapy** needs to start as **soon as possible after** your **stroke**

Who will see the information about me?

	We will keep the **information** about you **safe** **Only** the **researchers** will see the **information about you**
 	We may **share** your information with **other researchers** in this **country** We may **share** your information with **researchers** in **other countries** This **helps** with **other research** about **stroke** We will **take out your name** and **personal details**
	We will **tell your doctor** that you are taking part in this research project

What might be good about taking part?

	You **may be helped** by the physiotherapy
	You may **enjoy** taking part
	You may find it **interesting**
	You will help us to **learn** This may **improve recovery** for **other people** after **stroke**

What might be difficult about taking part?

	We **don't think** it is **unsafe** however the **therapy may not help** you
  	There **may be** some **side effects** You may find the **standing tiring** You may find **interview questions upsetting** It will **take** up **your time**

What if I don't take part in the research?

You will still get your **normal physiotherapy**

Is the research safe?

A **committee** said the research can happen

They say it is **safe**

They say that it has been **planned properly**

What if something goes wrong?

	This is very **unlikely** The NHS has set up a **committee** This committee will **check** the **research** The committee has **different people** from those who do this research
  	If you **take part** in the research and **if you think** you were **harmed** there are **people to talk to** **contact** xxxxx at **xxxx**

What will happen after the research?

	The **researchers** will **look at the results** They will **learn more** about **standing up early after stroke**

What will happen to the results?

	We will **tell you what we find out** from the research
  	We will share the **results** with **other researchers** at **conferences** and **meetings** in **academic journals** with **other people** who have a **stroke**
	The results will **not use your name**

What next?

	If you want to take part you will need to **sign** or **tick** ✓ a **consent form** This says that **you understand** the research and **you agree** to take part
 	You will have **an appointment** At this appointment you will have some **assessments** The appointment will **last for** approximately **60 minutes** Your **physiotherapy** will start **after** your **assessments** (probably the next day)

	**Yes** I want to
	No I don't want to

Appendix 11 Participant information sheet (for people with severe aphasia)

You've had a **stroke**

We're testing a **new physiotherapy idea**

SPIRES
STANDING PRACTICE IN REHABILITATION EARLY AFTER STROKE

Standing frame programme

\+ normal physiotherapy

Test

Normal physiotherapy

Test → Compare the results

5 – 7 days per **week** for **3 weeks**

NO

YES

You can decide to take part

Participant's Signature _____

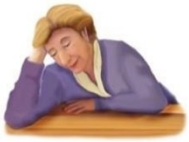
Participant's Name: _____

Participant Number: ☐ ☐ ☐ ☐ ☐

A4 Aphasia Friendly PIS page 1

What will I have to do?

Do some **exercises**



You may find these **tiring**

Have some **assessments**

Answer some **questions**

Share your **opinions** and **experiences**

All of your **information** will be kept **confidential**

A **committee** has said the research is **safe** and has been **planned properly**

Appendix 12 Work instruction for the intervention

1.0 Purpose of this document

This Work Instruction provides detailed instructions to achieve safety and consistency when implementing the functional standing frame programme and recording the content of the usual physiotherapy group for the SPIRES trial across the four sites.

2.0 Definitions

Orthostatic hypotension: a sustained drop in systolic blood pressure of at least 20mmHg and/or diastolic blood pressure of at least 10mmHg within three minutes of moving from supine or sitting into standing.

Brief questionnaire: This is a double-sided A4 sheet which contains visual analogue scales with pictures to ensure people with aphasia can use. The questionnaire asks participants to rate their perceived level of enjoyment, fatigue, effort and any aches or pains.

Physiotherapy Intervention Recording Tool: A checklist which physiotherapists can tick boxes to indicate specific activities undertaken during physiotherapy sessions for both the functional standing frame programme and usual physiotherapy interventions. For the functional standing frame programme, boxes will be provided for you to record the number of minutes the participant stood for, number of repetitions of sit to stand and any AEs.

3.0 Scope

This Work Instruction applies to all clinicians and support staff involved in the SPIRES trial in all four sites:

- Lanyon Stroke Rehabilitation Unit, Camborne and Redruth Community Hospital
- Woodfield Stroke Rehabilitation Unit, Bodmin Community Hospital
- Elizabeth Stroke Rehabilitation Unit, Bideford Community Hospital
- Skylark Stroke Rehabilitation Unit, Mount Gould Hospital

4.0 Responsibilities

The PIs and treating physiotherapists at each site are responsible for adhering to the Good Clinical Practice guidelines and undertaking the trial specific training delivered by the Chief Investigator, Angie Logan.

The Principal Investigators and treating physiotherapists at each site are responsible for the safe and appropriate use of the standing frame and ensuring all its component parts are fit and safe for purpose.

The Principal Investigators and treating physiotherapists at each site are responsible for ensuring each participant is medically stable and continues to meet the inclusion criteria before they undertake the functional standing frame programme.

5.0 Specific Procedure

Flow chart 1 demonstrates the procedure for implementing the functional standing frame programme for at least the first three sessions where monitoring of cardiovascular responses is required. This requires blood pressure to be taken and recorded whilst in bed (supine for at least 3 minutes) and taken again within 1 minute of being transferred into a chair. If no signs of orthostatic hypotension, the participant can be taken to the gym to begin their functional standing frame programme. If the participant demonstrates a drop in systolic blood pressure of at least 20mmHg and/or diastolic blood pressure of at least 10mmHg within three minutes of moving from supine or sitting into standing, please refer to the Orthostatic Hypotension protocol.

Flow chart 2 demonstrates the procedure for participants who have three consecutive blood pressure readings within the participant's normal range (≥ 90/60 to 120/80) where orthostatic hypotension was initially present but now resolved, or for those that do not have orthostatic hypotension.

Duration of standing

Thirty minutes' maximum, however, this should be graded. The aim is to incrementally increase this by 30% during every subsequent session until the 30 minutes is achieved. For example, if a participant stood initially for 7 minutes, then the subsequent session aims for a 9-minutes stand). However, if this is not

achievable, then a shortened increase in time based on the participants' ability should be implemented.

Repeated sit to stand

Aim for eight to 12 repetitions to facilitate strengthening, however, this should be graded. The aim is to incrementally increase this by 30% during every subsequent session until the maximum 12 is achieved. For example, if a participant achieved three sit to stands, then the subsequent session aims to achieve four. However, if this is not achievable, then a lower number of repetitions based on the participants' ability should be implemented.

Upper limb exercise and/or table top activities

These can be any activities that involve the hemi-plegic/paretic upper limb or both upper limbs. For example, muscle activation techniques; sensory input; facilitation of functional reach in tasks such as taking a drink, coming hair, washing face, table top games such as dominoes, Connect 4.

Reductions in postural support

Physiotherapists should use their clinical reasoning to progress the amount of postural support provided to participants by reducing the hip and trunk strap tension during standing and/or eliminating of the electronic power lifter for sit to stand.

Progression of participants

Should participants improve to the extent where support from the standing frame is not required, then unsupported standing/ walking can be progressed outside of the frame to optimise physical recovery for the remainder of the 3-week intervention if indicated. Repeated sit to stand (8–12 repetitions) should, however, be continued throughout the 30-minute session.

Use of foot sensors under feet

Customised foot sensors will be inserted under participants' feet. The aim is for the foot sensors to be used as biofeedback to encourage equal weight distribution during quiet standing and sit to stand. Participants are not expected to maintain equal weight distribution for the entire session, especially when undertaking table top activities. Physiotherapists will use their clinical reasoning to undertake any additional activities to facilitate equal weight distribution, and document this on the Physiotherapy Content Recording Tool. Physiotherapists will record the weight distribution during quiet standing at the beginning and end of each session.

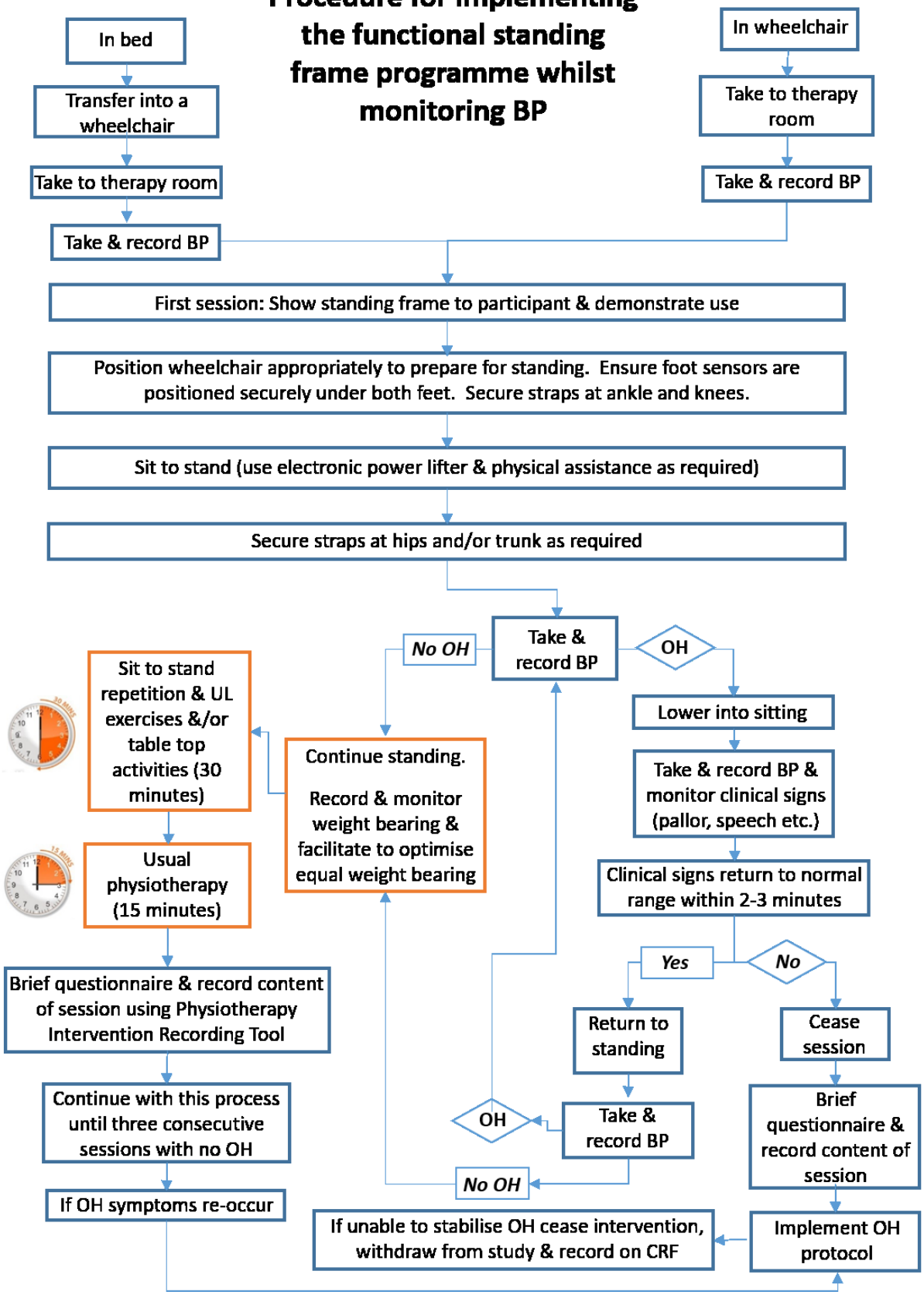
Please go to the SPIRES trial website: (https://www.plymouth.ac.uk/research/spires) which will include videos demonstrating standing, examples of how to progress the programme using case scenarios, downloadable schema of suggested task-specific exercises/ activities, advice on safety issues, what to do in the event of AEs and "frequently asked questions". It will also include trial details (e.g. background, rationale) and the CI's contact details. This will complement this SOP and the verbal training and support provided by the CI. A checklist of training undertaken by each of the treating physiotherapists will be recorded.

Recording the content of your physiotherapy sessions

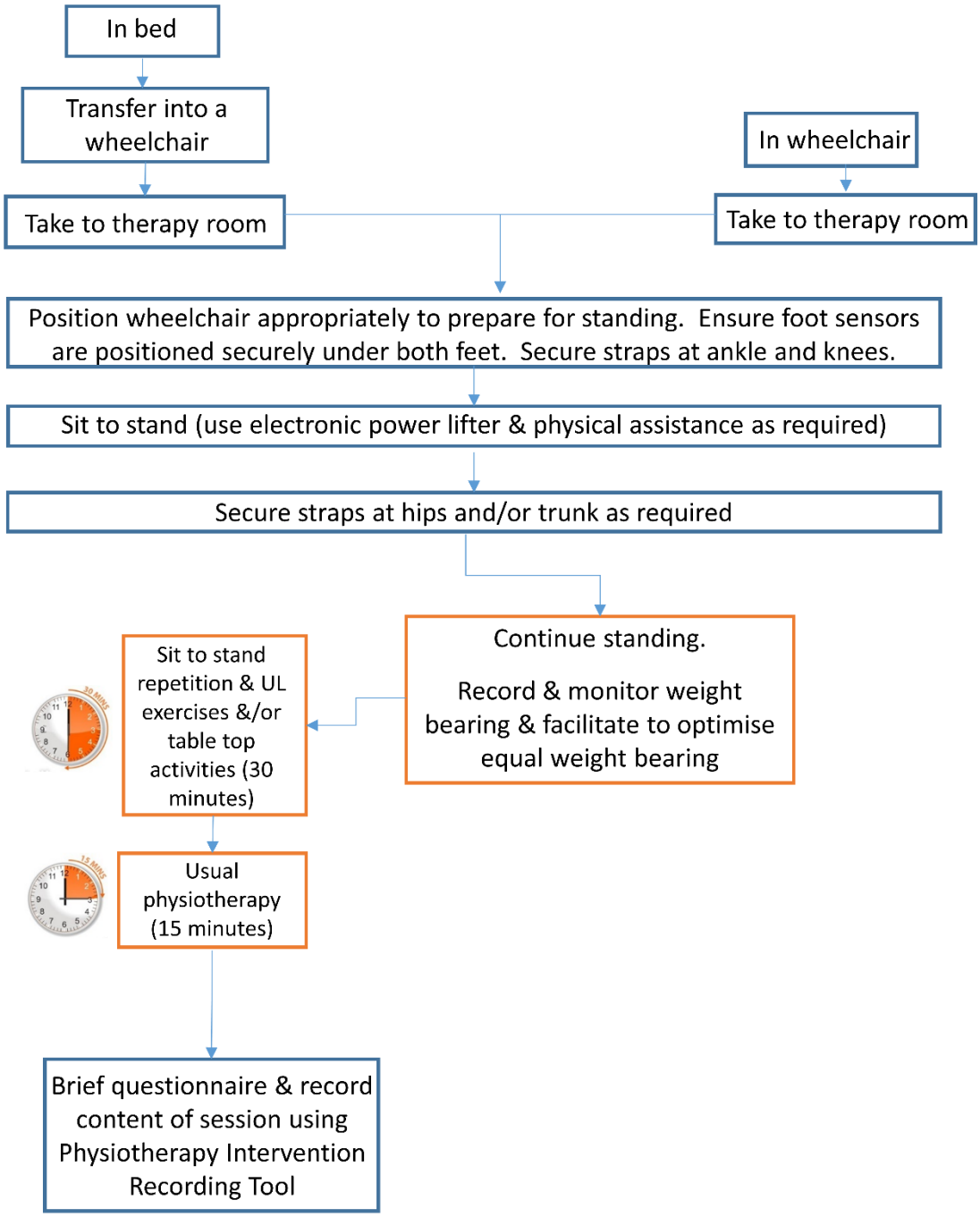
Please use the Physiotherapy Recording Tool (in the Case Report Form) to record the content of every session for both the functional standing frame programme and usual physiotherapy.

Flow chart 1
Procedure for implementing the functional standing frame programme whilst monitoring BP

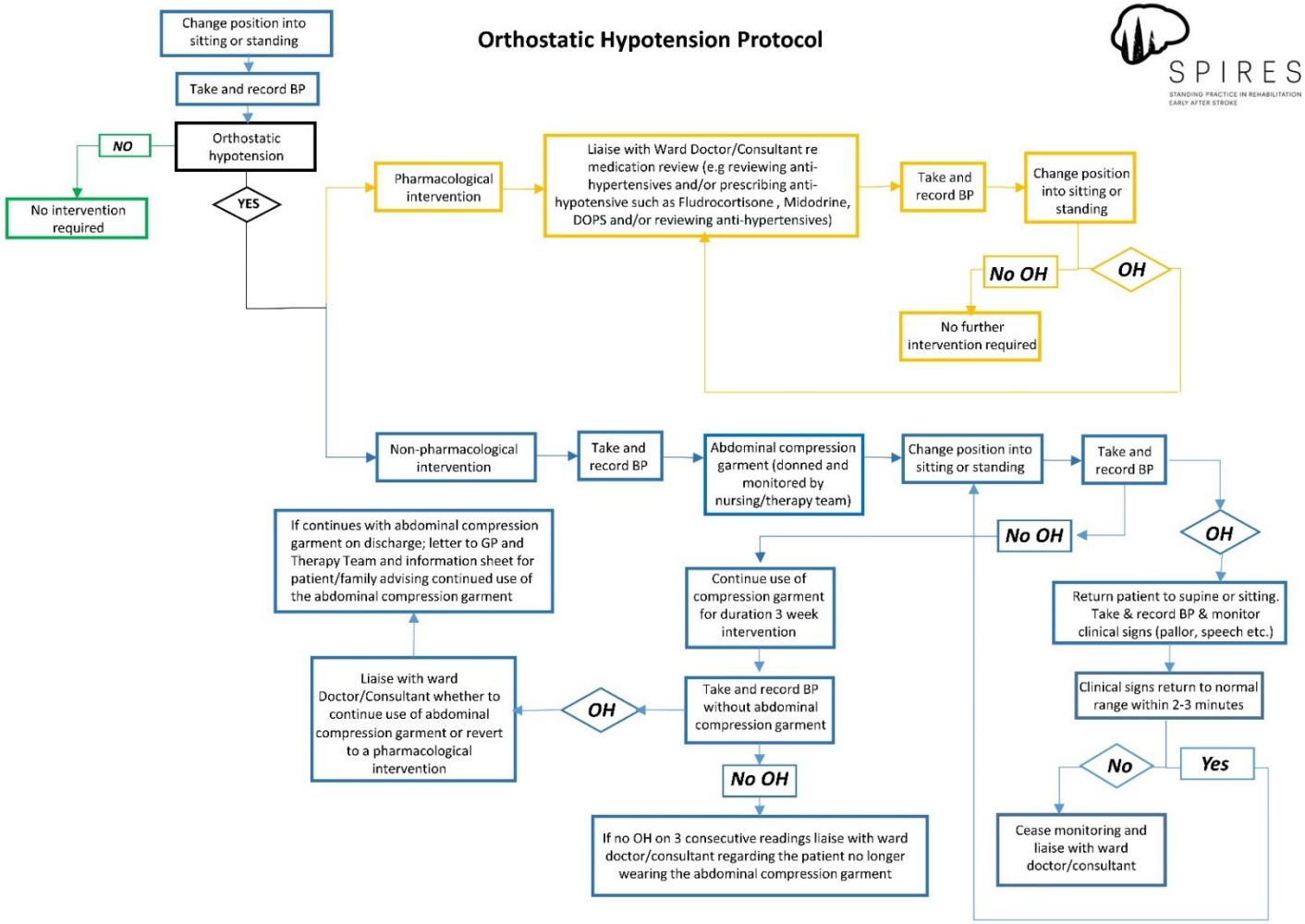
Version 1 12_07_2016



Flowchart 2
Procedure for implementing functional standing frame programme when OH stabilised



Appendix 13 Orthostatic hypotension protocol



Appendix 14 Treating therapist intervention Case Report Form

INTERVENTION PARTICIPANT STUDY NUMBER ☐☐☐☐☐

Week 1 Session 1 PARTICIPANT INITIALS ☐☐☐

SPIRES

PHYSIOTHERAPY SESSION DETAILS

Session date d d / m m / y y y y

Was session completed Yes ☐ No ☐

If No, please give reason

Did the participant experience OH? Yes ☐ No ☐

If Yes:

Did the participant receive treatment for OH? Yes ☐ No ☐ N/A ☐

If Yes, what was the treatment? Pharmacological ☐ Non-pharma ☐ N/A ☐

Did hypotension affect completion of session? Yes ☐ No ☐ N/A ☐

Please check for any Adverse Events, and record on the AE pages at the back of this CRF.

FUNCTIONAL STANDING FRAME USAGE

Number of sit to stand repetitions

Electronic power lift used Yes ☐ No ☐

Support traps used *Please tick all boxes that apply* Trunk ☐ Hips ☐ Knees ☐

Activities undertaken whilst in standing frame:
Please tick all boxes that apply

Table top games (dominoes, Connect 4, Jenga etc.) ☐

Functional upper limb activities (reach & grasp for objects such as cup, jug, cutlery, pen etc.) ☐

Activities to improve cognition/perception ☐

Activities to improve speech/communication ☐

Other (specify below) ☐

Total duration of stand (to nearest whole minute)

Total duration of session (in minutes)

Please continue on next page

NO STANDING FRAME

Gross position of patient during treatment activities used:
Please tick all boxes that apply

Supine	☐	Prone	☐	Side lying affected side	☐
Side lying unaffected side	☐	Supported sitting	☐	Supported standing	☐
Perch sitting	☐	Unsupported sitting	☐	Unsupported standing	☐
Prone standing	☐	4-point kneeling	☐	2-point kneeling	☐
Crook lying	☐				

Treatment activities:
Please tick all boxes that apply

Exercise to increase strength	☐	Exercise to increase cardiovascular fitness	☐	Exercise to improve co-ordination	☐
Upper limb tasks	☐	Facilitation of movement /muscle activation	☐	Soft tissue mobilisation	☐
Joint mobilisation	☐	Sensory stimulation	☐	Balance activities (static)	☐
Balance activities (dynamic)	☐	Functional tasks (e.g. sit to stand, wash/dress)	☐	Practising transfers	☐
Stepping/walking/ gait re-education	☐	Review/progress seating	☐	Positioning	☐
Tone management	☐	Oedema management	☐	Pain management	☐
Splinting techniques	☐	Orthotics	☐	Education/training for patient and family	☐

Other treatment activities:
Please tick all boxes that apply

Acupuncture	☐	Taping (e.g. ROCK/Kinesio Tape)	☐	Ultrasound	☐
Compression	☐	Warm water bathing	☐	Body weight support treadmill training	☐
Functional electrical stimulation	☐	Microstim	☐	Hydrotherapy	☐
Theraband	☐	Nintendo Wii or other virtual reality games	☐	Lycra/compression garments	☐
Other treatment (please specify)					

Please continue on next page

INTERVENTION PARTICIPANT STUDY NUMBER ☐☐☐☐☐

Week 1 Session 1 PARTICIPANT INITIALS ☐☐☐

SPIRES

BRIEF INTERVIEW ASSESSMENT

Using the scales on the laminated card, please tick ONE answer and if possible record the actual score

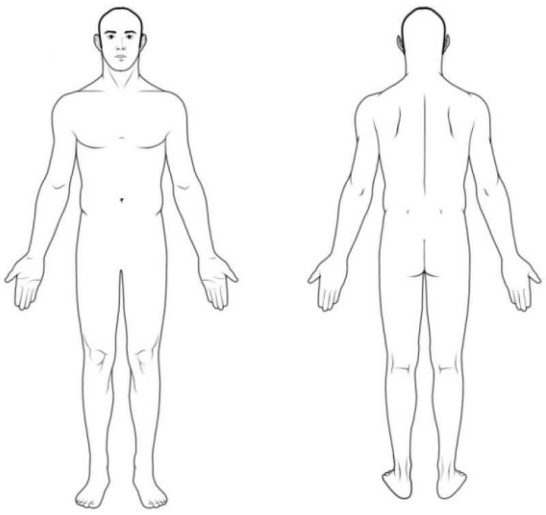
Enjoyment: Yes ☐ No ☐

Effort:
(0) None ☐ (1-3) Mild ☐ (4-6) Moderate ☐
(7-9) Severe ☐ (10) Unbearable ☐ Optional: What was the actual score ☐

Tiredness:
(0) Not at all tired ☐ (1-3) A little tired ☐ (4-6) Tired ☐
(7-9) Really tired ☐ (10) So tired, I can't do any ☐ Optional: What was the actual score ☐

Aches or Pains:
(0) None ☐ (1-3) Mild ☐ (4-6) Moderate ☐
(7-9) Severe ☐ (10) Worst pain possible ☐ Optional: What was the actual score ☐

Please mark on the body chart where the participant reports or indicates any aches or pains.



COMPLETED BY (CAPITALS) ☐

SIGNATURE ☐ DATE d d / m m / y y y y

Pages 2-4 represent one session and are repeated in the CRF to provide 21 sessions.

Appendix 15 Assessor Case Report Form (all timepoints are the same content)

3 WEEK PARTICIPANT STUDY NUMBER ☐☐☐☐☐

PARTICIPANT INITIALS ☐☐☐

SPIRES

Date of Visit d d / m m / y y y y

BARTHEL INDEX OF ACTIVITIES OF DAILY LIVING

Please tick one box per activity

Self-Reported ☐ Clinician Reported ☐

FEEDING

- Unable ☐
- Needs help cutting, spreading butter, etc., or requires modified diet ☐
- Independent ☐

BATHING

- Dependent ☐
- Independent ☐

GROOMING

- Needs to help with personal care ☐
- Independent face/hair/teeth/shaving (implements provided) ☐

DRESSING

- Dependant ☐
- Needs help but can do about half unaided ☐
- Independent (including buttons, zips, laces, etc.) ☐

BOWELS

- Incontinent (or needs to be given enemas) ☐
- Occasional accident ☐
- Continent ☐

Please continue to next page

BARTHEL INDEX OF ACTIVITIES OF DAILY LIVING: continued

BLADDER

- Incontinent, or catheterized and unable to manage alone ☐
- Occasional accident ☐
- Continent ☐

TOILET USE

- Dependent ☐
- Needs some help, but can do something alone ☐
- Independent (on and off, dressing, wiping) ☐

TRANFERS (BED TO CHAIR AND BACK)

- Unable, no sitting balance ☐
- Major help (one or two people, physical), can sit ☐
- Minor help (verbal or physical) ☐
- Independent ☐

MOBILITY (ON LEVEL SURFACES)

- Immobile or < 50 yards ☐
- Wheelchair independent, including corners, > 50 yards ☐
- Walks with help of one person (verbal or physical) > 50 yards ☐
- Independent (but may use any aid; for example, stick) > 50 yards ☐

STAIRS

- Unable ☐
- Needs help (verbal, physical, carrying aid) ☐
- Independent ☐

Please continue to next page

EDMANS ADL INDEX

Please tick one box per activity

Self-Reported ☐ Clinician Reported ☐

WASHING

Top half

- Needs full help ☐
- Washes face and chest only ☐
- Needs help to wash one arm and back only ☐
- Independent ☐

Lower half

- Needs help from 2 people ☐
- Stands with 1 person to wash own bottom ☐
- Stands with supervision to wash own bottom ☐
- Independent ☐

Bathing/shower

- Needs help from 2 or more people/bath hoist ☐
- Needs help from 1 person, not using bath hoist ☐
- Needs supervision only ☐
- Independent ☐

GROOMING

Comb hair

- Needs full help ☐
- Needs minimal help ☐
- Needs supervision only ☐
- Independent ☐

Please continue to next page

EDMANS ADL INDEX: continued

Clean teeth (own or dentures)

- Needs full help ☐
- Needs minimal help ☐
- Needs supervision only ☐
- Independent ☐

Shave/make up

- Needs full help/stopped since illness ☐
- Needs minimal help ☐
- Needs supervision only ☐
- Independent ☐

DRESSING

Top half

- Needs full help ☐
- Needs help to put one arm into sleeve ☐
- Needs help with fastenings only ☐
- Independent ☐

Lower half (including standing up)

- Needs help from 2 people ☐
- Needs help from 1 person ☐
- Needs supervision only ☐
- Independent ☐

Please continue to next page

EDMANS ADL INDEX: continued

Shoes

- Needs help with both sides ☐
- Needs help with 1 shoe ☐
- Needs help with shoe fastenings ☐
- Independent ☐

MEAL TIMES

Swallowing

- Needs NG tube/PEG, special diet or full help ☐
- Needs minimal help ☐
- Needs supervision only ☐
- Independent ☐

Drinking (excluding swallowing problems)

- Needs full help ☐
- Needs minimal help ☐
- Needs supervision only ☐
- Independent ☐

Eating (excluding swallowing problems)

- Needs full help ☐
- Needs help to cut up food ☐
- Needs supervision only ☐
- Independent ☐

Please continue to next page

EDMANS ADL INDEX: continued

BASIC MOBILITY

Sitting

- Needs help from 2 or more people ☐
- Needs help from 1 person ☐
- Needs supervision only ☐
- Independent ☐

Standing

- Needs help from 2 or more people ☐
- Needs help from 1 person ☐
- Needs supervision only ☐
- Independent ☐

Transfers

- Needs help from 2 or more people or hoist ☐
- Needs help from 1 person ☐
- Needs supervision only ☐
- Independent ☐

ADVANCED MOBILITY

Walking (10 metres)

- Unable to walk ☐
- Walks with help from 1 person ☐
- Needs supervision only ☐
- Independent ☐

Please continue to next page

EDMANS ADL INDEX: continued

Stairs

- Unable to climb stairs ☐
- Climbs stairs with help from 1 person ☐
- Needs supervision only ☐
- Independent ☐

Getting up from the floor

- Needs help from 2 or more people / hoist ☐
- Needs help from 1 person ☐
- Needs supervision only ☐
- Independent ☐

BED MOBILITY

Getting into bed

- Needs help from 2 or more people / hoist ☐
- Needs help from 1 person ☐
- Needs supervision only ☐
- Independent ☐

Moving around in bed

- Needs help from 2 or more people / hoist ☐
- Needs help from 1 person ☐
- Needs supervision only ☐
- Independent ☐

Please continue to next page

EDMANS ADL INDEX: continued

Getting out of bed

- Needs help from 2 or more people / hoist ☐
- Needs help from 1 person ☐
- Needs supervision only ☐
- Independent ☐

KITCHEN ACTIVITIES

Making a hot drink

- Dependent / not yet assessed ☐
- Needs minimal help ☐
- Needs supervision only ☐
- Independent ☐

Making a snack

- Dependent / not yet assessed ☐
- Needs minimal help ☐
- Needs supervision only ☐
- Independent ☐

Making a meal

- Dependent / not yet assessed ☐
- Needs minimal help ☐
- Needs supervision only ☐
- Independent ☐

Please continue to next page

EDMANS ADL INDEX: continued

HOUSEWORK ACTIVITIES

Basic cleaning

- Dependent / not yet assessed ☐
- Needs minimal help ☐
- Needs supervision only ☐
- Independent ☐

General laundry

- Dependent / not yet assessed ☐
- Needs minimal help ☐
- Needs supervision only ☐
- Independent ☐

Ironing

- Dependent / not yet assessed ☐
- Needs minimal help ☐
- Needs supervision only ☐
- Independent ☐

Please continue to next page

EDMANS ADL INDEX: continued

ASSOCIATED PROBLEMS

Please tick one box per problem

Does the patient have any of the following problems?

Language problems	Yes	☐	No	☐
Perceptual problems	Yes	☐	No	☐
Sensory problems	Yes	☐	No	☐
Dyspraxia problems	Yes	☐	No	☐
Reasoning problems	Yes	☐	No	☐
Memory problems	Yes	☐	No	☐
Depression problems	Yes	☐	No	☐
Anxiety problems	Yes	☐	No	☐
Urinary continence problems	Yes	☐	No	☐
Faecal continence problems	Yes	☐	No	☐

Please continue to next page

KNEE EXTENSORS STRENGTH

Using hand held dynameter

Knee extensors strength	Quadriceps left (Newtons)	Quadriceps right (Newtons)
Trial 1		
Trial 2		
Trial 3		

JOINT RANGE OF MOVEMENT

Using goniometry

Joint	Left (degrees)	Right (degrees)
Hip flexion angle (hip flexor length) Measured in side lying from 0 degrees		
Popliteal angle (hamstrings length) Measured in supine from 0 degrees		
Ankle plantar flexion Measured in supine from plantar grade = 0 degrees Normal range 0-50 plantarflexion		
Ankle dorsal flexion Measured in supine from plantar grade = 0 degrees Normal range 0-20 dorsiflexion		

Please continue to next page

MODIFIED ASHWORTH SCALE FOR MUSCLE TONE

If testing a muscle that primarily flexes a joint, place the joint in a maximally flexed position and move to a position or maximal extension over one second (count “one thousand one”)

If testing a muscle that primarily extends a joint, place the joint in a maximally extended position and move to a position of maximal flexion over one second (count "one thousand one”)

Score based on the classification below

0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of movement
2	More marked increase in muscle tone through most of the range of movement, but affected part(s) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

Using the score classification above, please place ONE score in each of the boxes below:

Hip adductors left	☐	Hip adductors right	☐
Hamstrings left	☐	Hamstrings right	☐
Ankle flexion left	☐	Ankle flexion right	☐
Ankle extension left	☐	Ankle extension right	☐

Please continue to next page

THE TRUNK CONTROL TEST FOR MOTOR IMPAIRMENT AFTER STROKE

The Trunk Control Test can be used to assess the motor impairment in a patient who has had a stroke. It correlates with eventual walking ability.

Testing done by patient lying on bed:

1) Roll to weak side
2) Roll to strong side
3) Balance in sitting position on the edge of the bed with the feet off the ground for at least 30 seconds
4) Sit up from lying down

Score based on the classification below

0	unable to do without assistance
12	able to do so using nonmuscular help or in an abnormal style; uses arms to steady self when sitting
25	able to complete task normally

Using the score classification above, please place ONE score in each of the boxes below:

1) Roll to weak side ☐
2) Roll to strong side ☐
3) Balance in sitting position on the edge of the bed with the feet off the ground for at least 30 seconds ☐
4) Sit up from lying down ☐

Please continue to next page

PHQ-9

Does the participant have aphasia?

Yes ☐ Yes, but is ABLE to complete ☐ No ☐

IF YES, please leave the questionnaire below blank and proceed to the SADQ-10 in the next section.

IF NO or ABLE, please complete the PHQ-9 questionnaire below. *Please circle one answer per question*

Over the last 2 weeks, but since your stroke only, how often have you been bothered by any of the following problems? *Please circle one answer per question*

	Not at all	Several days	More than half the days	Nearly every day
Little interest or pleasure in doing things	0	1	2	3
Feeling down, depressed, or hopeless	0	1	2	3
Trouble falling or staying asleep, or sleeping too much	0	1	2	3
Feeling tired or having little energy	0	1	2	3
Poor appetite or overeating	0	1	2	3
Feeling bad about yourself or that you are a failure or have let yourself or your family down	0	1	2	3
Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people? *Please tick one answer below*

☐ Not difficult at all ☐ Somewhat difficult ☐ Very difficult ☐ Extremely difficult

Please continue to next page

SADQ10

Does the participant have aphasia?

Yes ☐ No ☐

IF YES, please complete the SADQ10 questionnaire below. *Please circle one answer per question*

IF NO, please leave the questionnaire below blank and proceed to the SAQOL-39 in the next section.

	Often	Sometimes	Rarely	Never
Does he/she have weeping spells?	1	2	3	4
Does he/she have restless disturbed nights?	1	2	3	4
Does he/she avoid eye contact when you talk to him/her?	1	2	3	4
Does he/she burst into tears?	1	2	3	4
Does he/she indicate suffering from aches and pains?	1	2	3	4
Does he/she get angry?	1	2	3	4
Does he/she refuse to participate in social activities?	1	2	3	4
Is he/she restless and fidgety?	1	2	3	4
Does he/she sit without doing anything?	1	2	3	4
Does he/she keep him/herself occupied during the day?	1	2	3	4

Please continue to next page

SAQOL-39

Please circle one answer per question

DURING THE PAST WEEK

How much trouble did you have..	Couldn't do it at all	A lot of trouble	Some trouble	A little trouble	No trouble at all
preparing food?	1	2	3	4	5
getting dressed?	1	2	3	4	5
taking a bath or shower?	1	2	3	4	5
walking?	1	2	3	4	5
keeping your balance when bending over or reaching?	1	2	3	4	5
climbing stairs?	1	2	3	4	5
walking without stopping to rest or using a wheelchair without stopping to rest?	1	2	3	4	5
standing?	1	2	3	4	5
getting out of a chair?	1	2	3	4	5
doing daily work around the house?	1	2	3	4	5
finishing jobs that you started?	1	2	3	4	5
writing or typing, *i.e. using your hand to write or type*?	1	2	3	4	5
putting on socks?	1	2	3	4	5
doing buttons?	1	2	3	4	5
doing a zip?	1	2	3	4	5
opening a jar?	1	2	3	4	5
speaking?	1	2	3	4	5

Please continue to next page

SAQOL-39: continued

DURING THE PAST WEEK

How much trouble did you have..	Couldn't do it at all	A lot of trouble	Some trouble	A little trouble	No trouble at all
speaking clearly enough to use the phone?	1	2	3	4	5
getting other people to understand you?	1	2	3	4	5
finding the word you wanted to say?	1	2	3	4	5
getting other people to understand you even when you repeated yourself?	1	2	3	4	5
have to write things down to remember them, *(or ask somebody else to write things down for you to remember)?*	1	2	3	4	5
find it hard to make decisions?	1	2	3	4	5
feel irritable?	1	2	3	4	5
feel that your personality has changed?	1	2	3	4	5
feel discouraged about your future?	1	2	3	4	5
have no interest in other people or activities?	1	2	3	4	5
feel withdrawn from other people?	1	2	3	4	5
have little confidence in yourself?	1	2	3	4	5
feel tired most of the time?	1	2	3	4	5
have to stop and rest often during the day?	1	2	3	4	5
feel too tired to do what you wanted to do?	1	2	3	4	5
feel that you were a burden to your family?	1	2	3	4	5

Please continue to next page

SAQOL-39: continued

DURING THE PAST WEEK

How much trouble did you have..	Couldn't do it at all	A lot of trouble	Some trouble	A little trouble	No trouble at all
feel that your language problems interfered with your family life?	1	2	3	4	5
go out less often than you would like?	1	2	3	4	5
do your hobbies and recreation less often than you would like?	1	2	3	4	5
see your friends less often than you would like?	1	2	3	4	5
feel that your physical condition interfered with your social life?	1	2	3	4	5
feel that your language problems interfered with your social life?	1	2	3	4	5

Please continue to next page

EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health **TODAY**.

Mobility

- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

Self-care

- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

Pain/Discomfort

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

Anxiety/Depression

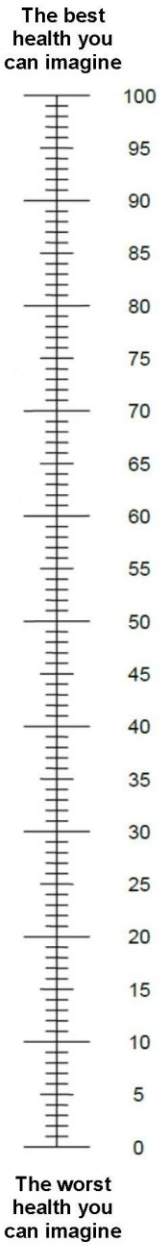
- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

Please continue to next page

EQ-5D-5L: continued

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Please continue to next page

ASSESSMENT OF FATIGUE

Using the scale on the laminated card, please tick ONE answer and if possible record the actual score

(0-3) No or minimal fatigue ☐ (4-10) Fatigue ☐

Optional: What was the actual score eg 6, or the range eg Tired or 4-6 ☐

INADVERTENT UNBLINDING

Has the Assessor been unblinded during this visit? Yes ☐ No ☐

If Yes, please provide a brief explanation ☐

If you had to guess, what group do you think the participant has been allocated to? Intervention ☐ Usual care ☐

ADVERSE EVENTS

No	Adverse event	Start date (enter NK in dd, mm and/or yyyy fields if date is uncertain)	Stop date [a] (enter NK in dd, mm and/or yyyy fields if date is uncertain)	Severity: Mild	Severity: Moderate	Severity: Severe	Is the event serious? [b]: Yes	Is the event serious? [b]: No
1		dd/mm/yyyy	dd/mm/yyyy					
2		dd/mm/yyyy	dd/mm/yyyy					
3		dd/mm/yyyy	dd/mm/yyyy					
4		dd/mm/yyyy	dd/mm/yyyy					
5		dd/mm/yyyy	dd/mm/yyyy					

a) Stop date: if AE is unresolved at session, leave stop date blank and review at next session
b) Is the event serious?: **If yes, complete an SAE form.**

VISIT SIGN OFF

COMPLETED BY (CAPITALS) ☐

SIGNATURE ☐ DATE d d / m m / y y y y

Please now:

- **Photocopy all pages and file the copy in the participant's study folder.**
- **Please return the original to PenCTU in the Freepost envelope.**

Appendix 16 Fidelity checklists

FIDELITY CHECK LIST FOR INTERVENTION GROUP

It is important that physiotherapists are following the steps in this checklist when implementing the functional standing frame programme with participants. These steps are detailed in the Work Instruction which accompanies the trial protocol.

Place a ✓ in the appropriate box on completion of each step and add any comments as appropriate.

Participant Number: ☐☐☐☐☐ **Initials:** ☐☐☐

Name of Observer: _____

Name of treating physiotherapist: _____

Date of observed session: _ _ / _ _ / _ _

ACTION	YES	NO	ADDITIONS/COMMENTS/ REASON FOR NOT COMPLETING
1. Physiotherapist(s) checks participant's blood pressure			
2. Physiotherapist(s) transfers participant into wheelchair if they are in bed			
3. Physiotherapist(s) show participant the standing frame and explain how it works if this is first session			
4. Physiotherapist(s) ensure foot sensors are positioned appropriately in the frame			
5. Physiotherapist(s) position participant in frame. If in wheelchair ensure footplates off, brakes on. If on therapy plinth ensure appropriately supported and plinth brakes on.			
6. Physiotherapist(s) adjust knee block/straps to level of tibial tuberosity in sitting			
7. Physiotherapist(s) fasten ankle strap			
8. Physiotherapist(s) fasten knee strap			
9. Physiotherapist(s) position and fasten belt for electronic power lifter			
10. Physiotherapist(s) facilitates/assists participant from sitting to standing ensuring hemiplegic upper limb is fully supported			
11. Physiotherapist(s) fasten hip/trunk straps as required			
12. Physiotherapist(s) check blood pressure if this is this is session 1-3 or if blood pressures have not yet stabilised in sit to stand			

13. Physiotherapist(s) facilitates participant to undertake activities in standing			
14. Physiotherapist(s) facilitates participant to undertake repeated sit to stand aiming for 8-12 repetitions			
15. Physiotherapist(s) explains progression of standing time and repeated sit to stand			
16. Physiotherapist(s) follows safe and appropriate procedures for sitting the participant down			
17. Physiotherapist records number of sit to stand repetitions in Case Report Form			
18. Physiotherapist records duration of standing time in Case Report Form			
19. Physiotherapist undertakes brief interview with participant using the aphasia friendly Visual Analogue Scales			
20. Physiotherapist explain potential adverse events e.g. muscle stretch pain, fatigue.			
20. Physiotherapist(s) undertakes 15 minutes of usual physiotherapy with participant			
21. Physiotherapist documents activities undertaken in usual physiotherapy time			
22. Physiotherapist documents if participant is receiving any treatment of Orthostatic Hypotension			
23. Physiotherapist documents reasons why participant was unable to take part in today's session and, if appropriate, records Adverse Events in the relevant section of the Case Report Form.			
22. Physiotherapist checks for adverse events and records appropriately.			

Comments:

FIDELITY CHECK LIST FOR CONTROL GROUP

It is important that physiotherapists are following the protocol and documenting activities undertaken in the usual physiotherapy sessions in the Case Report Forms.

Place a ✓ in the appropriate box on completion of each step and add any comments as appropriate.

Participant Number: ☐☐☐☐☐ ☐☐☐
nitials:

Name of Observer: _____

Name of treating physiotherapist: _____

Date of observed session: _ _ / _ _ / _ _

ACTION	YES	NO	ADDITIONS/COMMENTS/ REASON FOR NOT COMPLETING
1. Physiotherapist(s) undertake usual physiotherapy with participant			
2. Physiotherapist documents activities undertaken in usual physiotherapy session			
2. Physiotherapist documents if participant is receiving any treatment of Orthostatic Hypotension			
3. Physiotherapist documents reasons why participant was unable to take part in today's session if appropriate and records any adverse events in the Adverse Event section of the Case Report Form.			
4. Physiotherapist documents duration of session			
5. Physiotherapists are adhering to the trial protocol and not implementing a standing frame programme			

Comments:

Appendix 17 Topic guides for interviews and focus group

Participants' Topic Guide

Main question	Possible probes
Aims: to understand what led you to decide to participate in the study	
• Can you tell me why you agreed to take part in this study?	
• How were you approached by the clinical and research staff to participate in the study?	What interested you about the study?
• What is your understanding of about the study?	
• What were your thoughts about the amount and complexity of information about the study?	
Aims: to understand the communication between you and research team	
• What did you think about the information that was given to you about the study?	Was it clear?
• What do you think about the communication between you and the research team?	Was it good, satisfactory, poor?
• What are your thoughts do you think about the communication between you and the physiotherapists who treated you?	Was it good, satisfactory, poor?
• **What, if anything, could have made it better?**	
Aims: to understand how you felt about being randomised in to a particular group	
• How do you feel about being in the usual physiotherapy group? Would this influence your decision to be involved in future research studies?	Would you agree to participate in another research study in the future if there was a chance that you wouldn't get allocated to the group you preferred?

• What were your reasons for staying in the study even though you were randomised into the usual physiotherapy group? [*omit as appropriate*] • How do you feel about being in the functional standing frame programme group? Would this influence your decision to be involved in future research studies? • Did you have a preference for a particular treatment?	

Main questions	Possible probes
Aims: to understand participants' overall experience of the functional standing frame programme	
• What was your overall experience of the functional standing frame programme? • Was there anything you liked about the standing frame programme? • Was there anything you didn't like about the standing frame programme? • Would you agree to take part in it again if it were offered to you?	Did you enjoy it? Why did you like/not like it? Do you think 30 minutes was too long to be using the frame or about right?

• Talk to me about what it as like physically standing and practising standing up and sitting down?
  ○ Any muscle aches and pains during or after?
  ○ Fatigue during or after?
  ○ Did you experience any other issues similar to those you've already mentioned?
	Did you experience any muscle soreness or other aches and pains during or after the standing frame programme?

• Do you have suggestions about how we could change or improve the standing frame programme?	

Main questions	Possible probes
Aims: to understand what participants though about the study assessments • What did you think of study assessments? • What did you like about the study assessments? • What did you dislike about the study assessments? • Do you have suggestions to change or improve the study assessments?	Were they easy to complete? Were they challenging to complete? Were there too many different tests? Were they carried out too frequently or about right? Did you find them tiring? Were there too many or about right?

Topic guide for people who declined to participate in the study

Main questions	Possible probes
Aims: to understand why people do not want to participate in the study • What were your reasons for not wanting to participate in the study? • Do you feel the study was explained clearly to you? • What were your understandings of the study? • What were your thoughts about the amount of information about the study? • What were your thoughts about being asked to be involved in our research study?	Did they say anything that you didn't like or that concerned you? Did you read the Participant Information Sheet? What do you think about it? Was it easy to read? Too much information? Not enough information? Approached at the wrong time?

Topic guide for people who withdrew from the study

People who withdrew from the study	
• What was your overall experience of the study? • Can you tell me why you decided to stop the research study? • Do you think you knew enough about the study before agreeing to participate? • Did you speak to your family about agreeing to participate in the study? • Did you speak to anyone about stopping the research study? • What were your thoughts about how information about the study was presented to you? • What do you think about the idea of the functional standing frame programme?	Was there anything that you enjoyed? Was there one specific reason for deciding to withdraw or several? E.g. family, clinical care team, researcher? Thoughts about Participant Information Sheet. Easy to read? What about the person who approached you about participating in the study? Good idea? Too difficult/challenging?

Relatives' Topic Guide

Carers' perspectives	
• How do you feel about your husband/wife/mum/dad participating in the research study? • What are your thoughts and feelings about your husband/wife/mum/dad being randomised into one of two different physiotherapy treatment groups? • What support or advice did you offer your husband/wife/mum/dad in agreeing or declining to participate in the study? • What support or advice did you offer your husband/wife/mum/dad throughout the research study? • You were asked to be a consultee to provide advice on behalf of your husband/wife/mum/dad (agree for them to participate in the research study)… what are your thoughts about the consent process? [*for consultees only*] • What is your understanding of what the study was about? • What do you think about the communication between the research team and you/your relative? • What do you think about the communication between the physiotherapists who undertook the standing frame sessions with your relative? • Do you have any suggestions about how we can change or improve the study?	Did you think it was a good/bad idea? Were you hoping that they would have been allocated into a particular group? Do you feel your relative needed support to agree to participate and complete the physiotherapy programme? Were you and your relative given enough information? Too much?

Clinicians' Topic Guide

Functional standing frame intervention	Prompts
• What is your overall experience of delivering the functional standing frame programme intervention? • What do you think about the standing frame as a treatment for people with stroke? • Do you feel there were specific things that made it easier or more difficult to implement the functional standing frame with people with severe stroke? • In your opinion, do you think this intervention is feasible/appropriate for people who have suffered a severe stroke?	Did you find it easy or challenging to implement? More suitable for a particular severity: mild, moderate or severe? Useful? Not useful? E.g. the level of ability/disability of the participants? Time? Resources? Training received or required related to implementing the functional standing frame programme?

Study processes	Prompts
• What are your thoughts about the design of the study? What do you think about a cluster RCT [explain this term]	Do you think it answered the research question?
• What did you think about the study protocol?	Easy to follow? Too much or too little information? Too strict? About right? Did you worry about breaching the protocol?
	Too strict? Too broad?
• What do you think about the study documentation? Do you have a preference for a specific PIS when introducing the idea of the research to potential participants/relatives?	Did you have to spend a lot of time talking about the study?
• What are your thoughts about the consent process? How much time did participants/relatives need/want to make decision to join/decline?	Too many? Unachievable? About right?
	Were you aware of the reasons why? Do you think there was anything you or the research team could have done to prevent this?
• What are your thoughts about participant inclusion and exclusion criteria?	
• What do you think about the communication between the research team and yourself?	Was the training and protocol helpful/useful?
• What do you think about communication between the participants, relatives and yourself?	
• What do you think about the number of participants required for the study?	Did you find it easy? Complicated? Time consuming?
• Did you have anyone drop out of the research study (from either group)?	

• Did you have any participants who you suggested to withdraw from the research study? Why? • What are your thoughts and feelings about the overall management of the study? • What would you suggest or recommend to change or improve the study? • What are your thoughts about the procedure for reporting adverse events?	

Research in clinical practice	
• What are your thoughts about implementing research in clinical practice?	Is implementing research into clinical practice important to you? Do you think research helps inform/change your clinical practice? Does it require a lot of time and effort? Do you think it's worth the time and effort?
• What are your thoughts and feelings about the impact of delivering this research on your workload?	Do you think implementing the functional standing frame programme has had an impact on your clinical practice? Do you think you would change your clinical practice as a result of being involved in delivering this research?

Appendix 18 Relative participant information sheet for interview

RESEARCH WITH PLYMOUTH UNIVERSITY

SPIRES
STANDING PRACTICE IN REHABILITATION EARLY AFTER STROKE

Consent Form – Carer/Relative Interview

Version 1: 12/07/2016 REC

Site Number: _____

Study Number: _____

Name of Researcher: _____

	Please initial each box
1. I confirm that I have read and understand the information sheet Version: _____ *dated* _____ for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my legal rights being affected.	☐
3. I understand that information collected about me during the study may be looked at by responsible individuals from the study organisers and regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my information.	☐
4. I consent to the storage of data, including personal information, for the purposes of this study on a password protected and encrypted Plymouth University computer. I understand that any information that could identify me will be kept strictly confidential and that no personal information will be included in the study report or other publication.	☐
5. I agree to take part in the above study	☐

_____	_____	_____
Name of participant	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature

When completed: 1 for participant and 1 for researcher site file (original)

Appendix 19 Physiotherapist participant information sheet for interview and/or focus group

RESEARCH WITH PLYMOUTH UNIVERSITY

SPIRES
STANDING PRACTICE IN REHABILITATION EARLY AFTER STROKE

Consent Form – Clinician Interview & Focus Group

Version 1: 12/07/2016 REC

Site Number: _____

Study Number: _____

Name of Researcher: _____

	Please initial each box
1. I confirm that I have read and understand the information sheet Version: _____ *dated* _____ for the I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my legal rights being affected.	☐
3. I understand that information collected about me during the study may be looked at by responsible individuals from the study organisers and regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my information.	☐
4. I consent to the storage of data, including personal information, for the purposes of this study on a password protected and encrypted Plymouth University computer. I understand that any information that could identify me will be kept strictly confidential and that no personal information will be included in the study report or other publication.	☐
5. I agree to take part in the above study	☐

Name of participant	Date	Signature

Name of person taking consent	Date	Signature

When completed: 1 for participant and 1 for researcher site file (original)

Appendix 20 Patient consent form

RESEARCH WITH PLYMOUTH UNIVERSITY

SPIRES
STANDING PRACTICE IN REHABILITATION EARLY AFTER STROKE

Consent Form

Version 1: 12/07/2016 REC

Site Number: _____

Study Number: _____

Name of Researcher: _____

Please initial each box

1. I confirm that I have read and understand the information sheet Version: _____ *dated* _____ for the I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of any of my medical notes and information collected about me during the study may be looked at by responsible individuals from my local NHS Trust, the study organisers and regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records ☐
4. I consent to the storage of data, including personal information, for the purposes of this study on a password protected and encrypted Plymouth University computer. I understand that any information that could identify me will be kept strictly confidential and that no personal information will be included in the study report or other publication. ☐
5. I agree to my GP being informed of my participation in the study ☐
6. I agree to take part in the above study ☐

_____	_____	_____
Name of patient	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature

When completed: 1 for patient, 1 for medical record (original), 1 for researcher site file

Appendix 21 Consultee declaration form and information sheet

RESEARCH WITH PLYMOUTH UNIVERSITY

SPIRES
STANDING PRACTICE IN REHABILITATION EARLY AFTER STROKE

Consultee Declaration Form

Version 1: 12/07/2016 REC

Centre Number: _____

Study Number: _____

Patient Identification Number for this trial: _____

Name of Researcher: _____

	Please initial each box
1. I _____ [name of consultee] have been consulted about _____ [name of potential participant]'s participation in this research project. I have had the opportunity to ask questions about the study and understand what is involved.	☐
2. In my opinion he/she would have no objection to taking part in the above study.	☐
3. I understand that I can request he/she is withdrawn from the study at any time, without giving any reason and without his/her care or legal rights being affected.	☐
4. I understand that relevant sections of his/her medical records will be accessed by the research team to gather information such as previous medical history and brain scan results.	☐
5. I agree to their GP or other care professional being informed of their participation in the study	☐

_____	_____	_____
Name of consultee	Date	Signature

_____ Relationship to participant

_____	_____	_____
Person undertaking consultation (if different from researcher)	Date	Signature

_____	_____	_____
Researcher	Date	Signature

When completed: 1 for consultee, 1 for medical record (original), 1 for researcher site file

RESEARCH WITH PLYMOUTH UNIVERSITY

SPIRES
STANDING PRACTICE IN REHABILITATION EARLY AFTER STROKE

Consultee Information Sheet

Version 1: 12/07/2016 REC

Introduction

You are being invited to act as a 'consultee' for your relative/friend who is unable to make a decision for themselves. You are being asked to advise the researcher about his/her wishes and feelings as to whether they themselves would have wished to participate in this research. Before you decide, it is important for you to understand what it means to be a consultee, as well as why the research is being done and what it will involve. Please take time to read this information carefully and ask us if anything is not clear or if you would like more information.

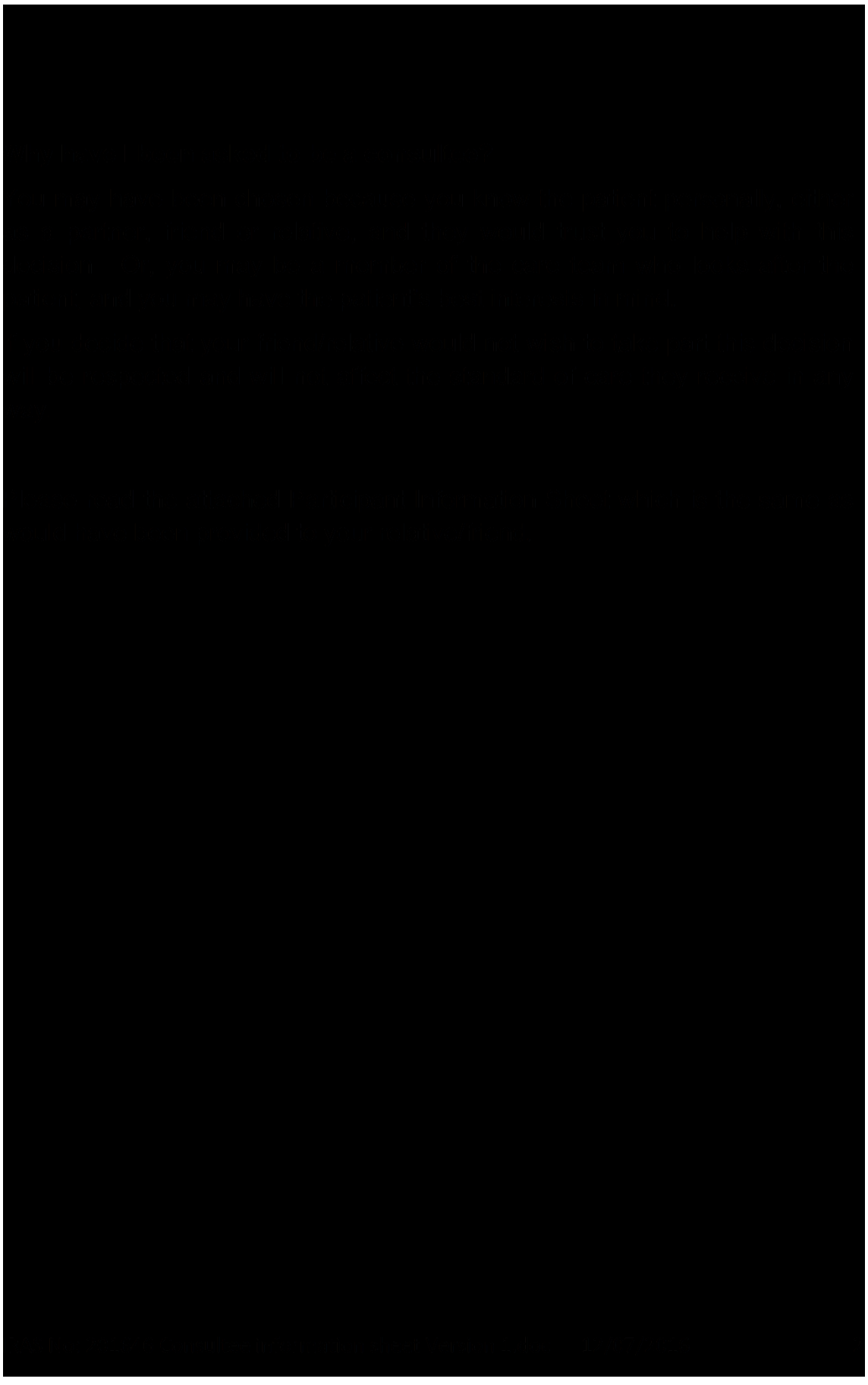
What does it mean to be a consultee?

A consultee is someone who knows a person who lacks the mental capacity to make the decision to participate in this research and is willing and able to offer an opinion as to what your relative/friend's wishes would be. Please let us know of any advance decisions they may have made about participating in research. These should take precedence.

If you decide your relative/friend would have no objection to taking part, we will ask you to read and sign the consultee declaration. We'll then give you a copy to keep. We will keep you fully informed during the study so you can let us know if you have any concerns or you think your relative/friend should be withdrawn.

We will not ask you to do anything else other than advise about your relative/friend participating in our research. You will not need to complete any assessments or paperwork on their behalf.

You do not have to act as a consultee if you do not want to.



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